

THE QUARTERLY JOURNAL OF MEDICINE

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VOLUME III

1909-10

27,885

OXFORD: AT THE CLARENDON PRESS

LONDON, EDINBURGH, NEW YORK, TORONTO & MELBOURNE: HENRY FROWDE.

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ON LEUKANAEMIA

By CHARLES H. MELLAND

With Plate 1

ONE comes fairly commonly across cases of anaemia and enlargement of the spleen without any increase in the number of leucocytes. In calling these all 'Splenic Anaemia' there is a risk of classing together cases of widely different pathology and requiring very different treatment.

One group has been satisfactorily defined, largely through Professor Osler's efforts, and to this group I would limit the name Splenic Anaemia. Here we have enlargement of the spleen, anaemia—often of only moderate degree—and a tendency to severe recurrent haemorrhages, particularly from the stomach. The cases are mostly chronic in character and the patients may live for many years, and eventually a cirrhosis of the liver supervenes and we have the terminal picture of Banti's Disease. The blood shows the features merely of a secondary anaemia with no distinguishing characters, beyond a fairly constant diminution in the leucocyte count, affecting particularly the polymorphonuclear cells and so resulting in a relative excess of lymphocytes. The disease appears to be one primarily limited to the spleen, and excision of the spleen has effected a cure in several cases in which it has been tried.

But occasionally cases are met with in which, with anaemia, enlargement of the spleen and no increase in the leucocytes, there are marked *qualitative* changes in both the red and white corpuscles which suggest those met with in leukaemia, and it is to some of these cases, particularly the more severe, in which the anaemia is most pronounced and the diminution of red corpuscles approaches or surpasses that met with in pernicious anaemia, that the name leukanaemia has been applied.

I think we shall be misleading ourselves if we attempt to regard these cases, as some have done, as presenting a true combination of the pathological conditions met with in pernicious anaemia and leukaemia. There is undoubtedly abnormal action of the bone-marrow and abnormal formation of red and white cells in it, but with a single exception—a case described by Hirschfeld—there is no evidence of the active blood destruction and consequent haemosiderosis of liver and kidney that is met with in pernicious anaemia. It appears quite plain to me that they should be regarded rather as atypical cases of leukaemia; and in many of the cases described, including the one

[Q. J. M., Oct., 1909.]

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that I have to record, there has been at one time or another a distinct increase in the leucocytes, sufficient to constitute a leukaemic condition.

I would indeed prefer to lay less stress on the anaemic aspect of the condition, since the insistence upon this as an important diagnostic point tends I am sure to separate artificially these cases from others to which they are pathologically closely allied, but in which the anaemia is less profound. I would suggest that if the name leukanaemia is to be retained it should be more widely applied so as to cover all those atypical cases in which there is plainly a leukaemia-like disease present without any or but very slight increase in the number of leucocytes.¹

The first description of a case in English medical literature was given by Parkes Weber in 1904, and he adopted the name coined by Leube as descriptive of a condition presenting the following features:—Progressive anaemia and asthenia with maintenance of the subcutaneous fat; changes in the red corpuscles rather similar to but not so extreme as those met with in true pernicious anaemia; absence of true leukaemic changes in the blood, but presence of slight myelocythaemia and of an inverted proportion of lymphocytes and polymorphonuclears. To these I would add the presence of large numbers of nucleated red corpuscles. Drysdale has recently published a case, with a *résumé* of recorded cases, and a reasoned conclusion as to the nature of the condition. I shall have further cause to refer to his valuable paper later, but I may state here that the conclusions at which I have arrived are substantially in accord with his.

With this much introduction I will proceed to describe the case on which my own observations have been based. The patient was a girl of 12 years and 8 months, who was first brought to see me at the Manchester Northern Hospital about the beginning of February, 1907. She was complaining of pain, which she placed in the epigastrium, and of swelling in the upper part of the abdomen. On examination there appeared to be some protuberance in the epigastrium, mainly due to her keeping the diaphragm rigidly contracted. She also kept the abdominal muscles firmly contracted, so that I was unable to make out any abnormality and dismissed her with a *placebo* to come back if she got any worse. She appeared perfectly healthy at that time. She was a Jewess and highly neurotic.

She returned in a month's time, with the account that she was worse rather than better, and then (March 2) there was quite evident enlargement of the left side of the abdomen, more noticeable in the lower part than in the upper, and in spite of the abdominal rigidity it was possible to make out a tumour which from its feel of elastic tension gave the impression of a tightly distended cyst and suggested an ovarian cyst or hydronephrosis. At this time she looked thinner and paler, but her colour was not such as to suggest any severe blood disease. She was advised to become an in-patient, and was

¹ Since writing this I see that Micheli, in a recent number of the *Folia Haematologica*, groups the various conditions, including leukanaemia, together in the same way.

admitted a week later under care of my surgical colleague, Mr. Roberts. In the interval she got rather rapidly worse, and a rough blood examination by my house physician, Mr. Leigh, on March 13, showed that she had only 1,600,000 red and 4,267 white corpuscles per c.mm. Mr. Roberts made an exploratory incision on March 14, and, finding at once that the tumour was an enlarged spleen, went no further but stitched up the wound, which healed by first intention, and transferred her back to my care. There was a distinct hæmorrhagic tendency, and the oozing of blood from the incision was only stopped with some little difficulty.

I saw her again on March 17. Her spleen was distinctly to be felt then, reaching down into the left iliac fossa and towards the middle line almost to the umbilicus. Her liver also was enlarged. She was very anaemic, though her colour was deceptive by reason of a pink flush on each cheek. Her temperature was high, 102.6° F., she was sweating profusely, her pulse was 144, small and very compressible. Her tongue was thickly furred; she was very thirsty, restless, and semi-delirious. She suggested at once to me the septicaemic picture of a case of acute leukaemia. There was no enlargement of any of the superficial lymph glands.

The examination of the blood on this date gave:—

Haemoglobin	26 %
Red corpuscles	1,265,000 per c.mm.
Haemoglobin index	111 %
Leucocytes	2,600 per c.mm.

The differential count of 500 leucocytes showed:—

Polymorphonuclear neutrophils	32 %	
Lymphocytes ²	{	small	.	.	47.2 %	} 56.4 %
	{	large	.	.	9.2 %	
Large mononuclears	7.6 %	
Eosinophils	0.2 %	
Basophils	0.2 %	
Myelocytes (neutrophil)	3.6 %	

119 nucleated red corpuscles were seen—equal to 619 in the c.mm.—and of these 19 were microblasts, 58 normoblasts, 13 megaloblasts, 23 intermediate, 4 free nuclei, and 2 metocytes. The red corpuscles appeared of about normal size and there was only a moderate degree of irregularity in size and shape, but much polychromatophilia and granular degeneration. There was an almost entire absence of the blood platelets.

Bearing in mind the frequency with which cases of acute leukaemia have had a history of septic tonsillitis I put her on ten-grain doses of sodii salicylat. and $\mathfrak{a}\text{iv}$ of liq. arsenicalis three times a day, the latter to be increased by

² I have retained the name lymphocytes in my classification throughout, though, as I shall show later, I have reason to believe that many of the cells so classified in this case are indifferent 'lymphoid' cells from the bone-marrow.

℥j per dose every day till a dose of ℥viij was reached, and then every other day up to ℥xij. At the same time she was put on liq. strychninae ℥iij and tinct. ferri perchlor. ℥x four times a day, and, as her bowels had been confined, she had grs. ij of calomel on the evening of March 19, with satisfactory results. My prognosis, however, was very grave, bearing in mind the unchecked course of other cases of a similar nature that I had had under my care, and I did not think that she was likely to outlast a week or ten days.

On March 24, a week later, the blood examination was again made :

Haemoglobin	36 %
Red corpuscles	1,540,000 per c.mm.
Haemoglobin index	113 %
Leucocytes	1,800 per c.mm.

The differential leucocyte count at this date will be found on reference to the accompanying Table. 70 nucleated red corpuscles were seen, equal to 378 per cubic millimetre, and of these 24 were microblasts, 30 normoblasts, 4 megaloblasts, 7 intermediate and 5 free nuclei. The red corpuscles showed a greater diversity of size and shape than on the previous examination, though the poikilocytosis was not extreme. There was a considerable proportion of large cells and the average size appeared larger than normal. Polychromatophilic corpuscles were numerous, granular red corpuscles only occasional. There was thus a slight improvement in nearly every respect, both the haemoglobin and the red corpuscle count having advanced, whilst the differential count of the leucocytes more nearly approached the normal; though, curiously enough, the diversity in size and shape of the red corpuscles was more marked. Fig. 1 is a field of the blood at this date.

During the next few days she steadily improved. Her temperature came down to normal on March 26, and although it ran up for a few days between March 29 and April 2, it never reached higher than 100° F. Her tongue was cleaner, her appetite very good, and her pulse on the evening of March 28 was for the first time below 100° F. By April 4 she had got up to ℥xi of liq. arsenicalis, and then, as she was going on so satisfactorily, it was reduced, the prescription of earlier date with its increasing doses being repeated, the object being to avoid the risk of toxic symptoms, with the necessity of stopping the drug when it was producing such satisfactory results. The blood examination on April 7 showed :—

Haemoglobin	60 %
Red corpuscles	3,830,000 per c.mm.
Haemoglobin index	70 %
Leucocytes	3,400 per c.mm.

The differential count of leucocytes can be read from the Table.

The improvement represented by the change in the blood was most striking: the red corpuscles had more than doubled in number in the course of a fortnight,

the varieties of leucocytes had returned to almost their normal relative figures, and the most markedly abnormal cells, the myelocytes and the nucleated red corpuscles, had both practically disappeared. The red corpuscles showed only very slight diversities in size and shape, and polychromatic and granular corpuscles were only rarely met with. The blood platelets too had returned in normal numbers.

By April 17 she had again worked up to her maximum dose, \mathcal{O} xij of liq. arsenicalis, without having been on any occasion sick with the medicine, so she was once more put back upon the smaller doses and the salicylate of soda and the mixture with strychnine and tinct. ferri perchlor. stopped and small doses of ferri et quininae cit. substituted.

During this time her general condition had improved commensurately with the improvement in her blood. Her temperature was normal, her appetite was good, she was regaining her strength and was beginning to get up. Her spleen, however, was larger than ever; it slowly and steadily increased till on April 25 it was found to extend down to within 1 inch of the pubic symphysis and reached $2\frac{1}{2}$ inches to the right of the middle line. The extreme length, measured from the costal margin, was $10\frac{1}{2}$ inches.

A blood examination was made on that date, April 25, and showed:—

Haemoglobin	70 %
Red corpuscles	4,350,000 per c.mm.
Haemoglobin index	80 %
Leucocytes	12,000 per c.mm.

The differential count of 500 leucocytes is shown in the Table. Ten nucleated red corpuscles were seen (equal to 240 per c.mm.), and of these 4 were microblasts, 1 normoblast, 2 megaloblasts, and 3 intermediate. The red corpuscles appeared normal in size and shape; there were a few polychromatophilic but no granular ones.

Although the haemoglobin and the number of red corpuscles had steadily continued to improve, there was thus very strong evidence in the large percentage of myelocytes (6.8 per cent.) and the inverted proportions of lymphocytes and polymorphonuclears (66.6 per cent. and 28.2 per cent.), as well as in the presence of numerous nucleated red corpuscles, that there was still grave disturbance of function in the blood-forming tissues. The child was so well, however, that, rather against my will, she was allowed to go home on April 29.

She was not, however, long outside; she soon appeared to be going downhill, although she was kept on small doses of arsenic; and so was again taken into hospital on May 8.

On examination she was found to have lost colour and to have become weaker. She had a number of petechiae scattered about her body and limbs, mostly of about the size of a split lentil or smaller, which she stated she first began to notice about the time that she left hospital. She had again developed pyrexia of an irregular type and sweated profusely at times. The dimensions

of the spleen were unaltered. The blood examination on May 10 confirmed the increase of anaemia which her appearance suggested. Her haemoglobin had fallen to 50 per cent. and the red corpuscles to 2,800,000 per c.mm. But the most striking change which the few days' interval had effected in the blood was in the leucocytes. On April 25 there had been a slight increase above the normal, but only up to 12,000 per c.mm.; now they had suddenly run up to 34,000. The change in the character of the corpuscles was as striking as that in the numbers.

In 1,000 leucocytes there were:—

Polymorphonuclear neutrophils	4.8 %	
Lymphocytes { small	40.9 %	} 93 %
{ large	52.1 %	
Large mononuclears	0.1 %	
Myelocytes	1.8 %	
Eosinophils	0.3 %	
Basophils	0.0 %	

Twenty-two nucleated red corpuscles were seen, equal to 783 in the c.mm., and of these 6 were microblasts, 3 normoblasts, 11 megaloblasts, and 4 intermediate—half of the total number being typical megaloblasts.

Thus there was a great increase in the total number of leucocytes, limited almost solely to the lymphocytes, and of these latter more than half were of the large type. On comparing these cells (Fig. 2) with those met with in acute leucocythaemia (Fig. 3) or with the cells in a case of spleno-medullary leukaemia with apparent change of type to the lymphatic form (Fig. 4) it is at once evident that they are identical. These cells we have come to regard as in no sense true lymphocytes derived from the lymphatic glands (Pappenheim, Weber, Melland), but rather as 'lymphoid' cells originating in the bone-marrow, either by an abnormally active proliferation of lymphoid cells pre-existing there or by a morbid return of the true myelocytes to a more primitive and embryonic phase in which they are unable to carry their differentiation to the extent of developing neutrophil granules in their protoplasm. The result is that we get large cells with a single round or oval nucleus centrally or slightly excentrically placed, with a rather narrow zone of cytoplasm surrounding it, staining diffusely with basic dyes, the periphery in many corpuscles more deeply than the rest, but containing no granules.

The child was put back on to the mixture containing ferri et quinae cit. grs. iv and liq. arsenicalis ℥ iv, the latter to increase as before, and on May 15 she was put on grs. v of salol, dissolved in 3j of liquid paraffin, three times a day. The temperature was somewhat erratic, but on no occasion did it reach beyond 101° F. at that time. The petechiae began to fade; she had two large ones on the left side of the tongue when readmitted, which had nearly gone after a fortnight's interval, and few, if any, fresh ones made their appearance. The measurement of the spleen showed no difference in its dimensions, though the abdomen appeared more prominent and the spleen more massive and

immovable. She put on a stone in weight in less than a fortnight after readmission, and I am inclined to attribute part of this at any rate to increase in bulk of the spleen. On May 18 it was first noticed that there was some swelling of glands on both sides of the neck—beneath the ear, below and within the angle of the jaw, in the substance of the parotid, and down the anterior and posterior triangles of the neck and in the supraclavicular region. They were mostly of small size, about that of peas or beans, soft and movable. Those on each side just below the ears were larger, as large as marbles. There were a few small glands in the left axilla, none palpable elsewhere. The child herself said she had noticed these lumps in the neck for several days. She was weaker and decidedly more anaemic, as was shown by the blood examination of May 19, from which it is seen that the condition had rapidly progressed for the worse. Her haemoglobin had fallen to 36 per cent. and the red corpuscles to 1,736,000 per c.mm., while the leucocytes had further increased to 74,400 per c.mm. Of these 98.2 per cent. were lymphocytes, the small being at this date more numerous than the large. The complete differential count is given in the accompanying synopsis of blood-findings.

As she was going down so steadily she was put on to the mixture of sod. salicylat. grs. xv and increasing doses of liq. arsenicalis under which she had improved so much on her first admission. But now it seemed to have lost its effect, for on examining the blood on May 28 there was a still further deterioration.

Haemoglobin	28 %
Red corpuscles	990,000 per c.mm.
Haemoglobin index	141 %
Leucocytes	29,400 per c.mm.

The lymphocytes still formed nearly 90 per cent. of the total number of leucocytes. The red corpuscles appeared on the average of about normal size, occasional macrocytes were present, no microcytes, and in shape they were mostly round or oval; there was certainly no marked degree of poikilocytosis. A few showed polychromatophilia and granular degeneration. The child was plainly weaker and more anaemic than she had ever been, her heart was dilating and her feet and legs were becoming oedematous. She was put on to tinct. ferri perchlor. α xv and quinae sulphat. grs. iv three times a day, in addition to the salicylate and arsenic mixture. For a while she seemed to improve, the anaemia became slightly less extreme, the oedema disappeared, and the glands in the neck became smaller. This temporary improvement was reflected in the blood. On June 5 she showed:—

Haemoglobin	34 %
Red corpuscles	1,820,000 per c.mm.
Leucocytes	12,400 „ „

The drop in the total leucocyte count had been accompanied by a rise in the polymorphs to 24.8 per cent. and a drop in the lymphocytes to 63 per cent.

There were still 7.6 per cent. of myelocytes and a large number, 520 per c.mm., of nucleated red corpuscles.

The improvement, however, was only temporary, and the last blood examination that was made, on June 25, showed:—

Haemoglobin	31%
Red corpuscles	1,260,000 per c.mm.
Leucocytes	24,000 „ „

Eighty per cent. of the leucocytes were classed as lymphocytes, the myelocytes were 4.2 per cent., and there were numerous nucleated red corpuscles, 1,258 per c.mm.

The child was again going downhill, and her progress now seemed entirely uninfluenced by treatment. For the last week her temperature had been continuously raised, touching or exceeding 101° F. on several occasions. From this date until her death on July 18 her temperature remained high, only coming down to normal on two occasions, running mostly, as the chart shows, above 102° F., frequently exceeding 103°, and on two occasions being over 104°. It was unfortunately impossible to get permission for a post-mortem examination.

There are several points of interest in the case. The nature of the disease to which the term leukanaemia has been applied has been much debated. It has been regarded by some as a disease *sui generis*, as a combination of pernicious anaemia and leukaemia, or as an aberrant, atypical form of leukaemia. A careful study of this case has convinced me that the condition is in reality an atypical leukaemia, and in this I am in full agreement with Drysdale in his paper in the first number of this Journal.

The disease in its clinical and haematological features most nearly resembles the acute form of leukaemia; indeed, some writers would include cases of acute leukaemia under leukanaemia as being more akin to the latter than to the more chronic forms of the disease. But this classification again fails fully to cover the facts. The majority of cases of acute leukaemia, with their excess of large lymphoid cells in the blood and bone-marrow, certainly present features but little resembling typical cases of myeloid leukaemia. But the difference is mainly a superficial one. A number of writers now (Weber, Pappenheim, Schultze, Veszprémi, Melland) have given good reasons for considering many of these 'lymphoid' cells as being derived from the bone-marrow, as being indeed as much myelocytes as those met with in the commonly named myeloid form, though primitive and imperfectly developed in character, with their typical granules wholly or largely undifferentiated. In some of the cases of the acute disease a careful examination of these cells (which most observers have been in the habit till recently of classing as lymphocytes) will show the development of a certain number of very sparsely scattered neutrophil granules, and in other cases again, as in the one described by Elder and Fowler, which had all the characteristic clinical features of acute leukaemia, a large proportion of the cells are definite neutrophil myelocytes.

It seems impossible, therefore, to draw a hard and fast line between the chronic and acute forms of leukaemia (vide also Gulland and Goodall), and both must be looked upon as mainly, if not wholly, of myelogenous origin. The pathological changes in the blood and the bone-marrow are in many cases similar and in some identical. Another intermediate form between them is presented by those rare cases in which as a terminal phase a fairly typical myelogenous leukaemia loses its characteristic eosinophil and neutrophil myelocytes, which are gradually replaced in the blood by undifferentiated 'lymphoid' cells (Fig. 4), having all the characters of those met with in the acute disease (Fig. 3), or in the case of leukanaemia I am at present describing (Fig. 2), but which are, there is little doubt, of myelogenous origin (Hirschfeld, Melland).

A differentiation of these cases of leukanaemia from true leukaemia is urged on account of the absence of increase in the eosinophils and basophils. Followers of Ehrlich have endeavoured to minimize the significance of the neutrophil myelocytes in the diagnosis of leukaemia and to lay stress on the eosinophils and basophils, which they state always show an enormous *absolute* increase, whereas in the atypical forms of leukaemia, amongst which I would include leukanaemia, these cells are actually *less* than normal, not only in percentage but in absolute numbers. The argument to my mind carries little weight; the plea is an endeavour to cling to Ehrlich's original and incorrect criterion of what constitutes leukaemia, and in those cases to which I have already referred, in which the character of the blood has changed from that of myelogenous leukaemia with, amongst others, numerous eosinophil and basophil cells, to one simulating lymphatic, that is, with an excess of 'lymphoid' cells, but with the disappearance of eosinophils, it cannot be held with any plausibility that the case has ceased to be one of leukaemia.

During the stage of the case of leukanaemia in which the number of leucocytes was small the diagnosis of pernicious anaemia was quite a possible one. The red corpuscles were greatly diminished, the haemoglobin index was over 100 per cent., and there was, as Fig. 1 shows, a certain degree of poikilocytosis and macrocytosis, though the irregularity in size and shape of the red corpuscles was not such as one would expect in a case of pernicious anaemia with the number of red corpuscles reduced to 1,265,000 per c.mm., nor, indeed, was it so great as appears to have been the case in several of the other cases of leukanaemia that have been recorded, in which it has been described as being fully as great as in the most pronounced case of pernicious anaemia. Large numbers of polychromatophilia and granular red corpuscles were also present. Yet all the while the enormous size of the spleen insistently pointed to some condition more closely allied to leukaemia than to pernicious anaemia. One has got to bear in mind that it has been repeatedly stated by competent observers, that in bothrioccephalus anaemia the blood picture is indistinguishable from that of pernicious anaemia, so that one must admit, though I have always been chary of doing so, that the blood changes that one looked upon as characteristic of true Addisonian anaemia may occasionally be met with in

other conditions. The absence of symptoms pointing to chronic inflammatory lesions of different regions of the alimentary tract and the absence in every case recorded, with one exception (Hirschfeld's), of any iron reaction in the liver strengthen the view that we have to do merely with a *simulation* of pernicious anaemia. We have got to remember further, as Drysdale points out, that in typical cases of chronic myeloid leukaemia we get a certain degree of irregularity in size and shape of the red corpuscles and marked abnormality in their staining capacities, so that it requires no great stretch of the imagination to picture all these conditions exaggerated in an allied acute disease which is severe from the onset and rapidly fatal.

In indicating a diagnosis of pernicious anaemia an altogether disproportionate stress has been laid upon the presence of large numbers of nucleated red corpuscles, many of them megaloblasts. Hurter, in whose case of leukanaemia there were 14,000 nucleated red corpuscles per c.mm., quotes Scott (Hon. G. H.) to the effect 'that megaloblasts are seen in the blood when the blood formation reverts to the embryonic type, i.e. only in pernicious anaemia', and accordingly classes his case as a combination of the blood conditions of leukaemia and pernicious anaemia. A more misleading statement it is impossible to imagine, as any one with any knowledge of the megaloblastic change both in the blood and bone-marrow in cases of myeloid leukaemia will at once admit. Speaking generally, nucleated red corpuscles of all types are more numerous in myeloid leukaemia than in pernicious anaemia.

It may appear to be a contradiction in terms to class a disease with an actual diminution in the number of leucocytes—there were only 1,800 per c.mm. on March 24—as a form of leukaemia, even if we qualify it by the term *atypical*. But experience has shown that characteristic cases of leukaemia may under treatment by arsenic or the X-rays, or as a result of intercurrent disease, temporarily lose their excess of leucocytes without it being possible to assert that they have ceased to be cases of leukaemia. Amongst a number of these I may mention one case under my own care in which the leucocytes were diminished to 800 per c.mm. under arsenical treatment, whilst a few weeks later they had again risen to some 70,000 per c.mm. When late on in my case of leukanaemia the number of leucocytes rose to 76,000 per c.mm. the character of the blood was practically indistinguishable from that of a case of acute leukaemia (Figs. 2 and 3), and but for the early leucopenia and the simulation of certain of the features of pernicious anaemia which has led some observers astray there would be no doubt as to its proper classification. I see no objection to the retention of the term leukanaemia to describe these cases so long as it is used to connote certain atypical leukaemia-like conditions, of similar general characters though often presenting considerable differences in detail, but not to imply any theory of the relation of the disease to pernicious anaemia.

Finally, a few words with regard to treatment may be of practical interest. The majority of cases that have been described as leukanaemia or as acute leukaemia have steadily progressed in spite of all treatment to a fatal

termination. Two cases (Teeter and Zevi) are described as having been cured, but I can learn little as to the treatment or the permanence of the cure. It is of much interest, therefore, that the case I have described improved very markedly for a time, and was indeed able to leave hospital and go home feeling and looking practically well, though still with evidence in her blood and in the size of the spleen that she was by no means cured. In the majority of cases arsenic, which, given in increasing doses, has frequently such a strikingly beneficial effect in the chronic cases of leukaemia, has proved of no value whatever. The high temperature, and the general appearance presented by the patient of one suffering from an acute infectious disease, suggested the use of those drugs which have been found to exercise an influence on septic infection, viz. salicylate of soda, quinine, and tinct. ferri perchlor. The improvement that resulted from this line of treatment was as gratifying as it was unexpected. To the eye the child appeared cured, though the abnormal cells still present in the blood and the undiminished size of the spleen led me to express a very cautious opinion as to the permanence of the cure. My fears were unfortunately fully justified, and when she came in a second time the treatment seemed to have almost wholly lost its efficacy.

Synoptical Table of Blood Examinations.

Date	Red corpuscles per cubic millimetre	Haemoglobin percentage	Leucocytes per cubic millimetre	Differential count of Leucocytes							Nucleated red corpuscles per c.mm.						
				Polymorpho-nuclear neutrophils	Lymphocytes		Large mononuclears	Myelocytes	Eosinophils	Basophils (mast cells)	Total number per c.mm.	Microblasts	Normoblasts	Megakaryoblasts	Intermediate	Free nuclei	Metarocytes
Mar. 17	1,265,000	26 %	2,600	32 % 832	47 % 1,222	9.2 % 239	7.6 % 197	3.6 % 93	0.2 % 5	0.2 % 5	619	99	298	69	122	20	11
Mar. 24	1,540,000	36 %	1,800	60.3 % 1,085	26.4 % 475	1.8 % 33	8.4 % 151	2.4 % 43	0.6 % 11	0.0 % 0	379	132	162	21	37	27	0
April 7	3,830,000	60 %	3,400	59.6 % 2,026	27.2 % 925	6 % 204	5.6 % 190	0.8 % 27	0.8 % 27	0.0 % 0	0	0	0	0	0	0	0
April 25	4,350,000	70 %	12,000	28.2 % 3,404	50.4 % 6,048	12.2 % 1,464	1.2 % 144	6.8 % 826	1 % 120	0.2 % 24	240	96	24	48	72	0	0
May 10	2,800,000	50 %	34,400	4.8 % 1,651	40.9 % 14,070	52.1 % 17,922	0.1 % 34	1.8 % 620	0.3 % 103	0.0 % 0	783	204	68	375	136	0	0
May 19	1,736,000	36 %	74,000	1.6 % 1,190	61.2 % 45,533	37 % 27,528	0.0 % 0	0.4 % 298	0.0 % 0	0.0 % 0	1,686	446	0	546	546	148	0
May 28	990,000	34 %	29,400	7.2 % 2,116	48.6 % 14,488	41.2 % 12,113	0.0 % 0	2.6 % 764	0.4 % 118	0.0 % 0	176	0	0	0	58	0	118
June 5	1,820,000	34 %	12,400	24.8 % 3,075	52.6 % 6,522	10.4 % 1,290	4.6 % 570	7.6 % 942	0.2 % 25	0.4 % 50	520	100	300	0	50	70	0
June 25	1,260,000	31 %	24,200	13.2 % 3,194	55.8 % 13,503	24.2 % 5,857	2.2 % 533	4.2 % 1,016	0.4 % 96	0.0 % 0	1,255	193	821	97	96	48	0

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PLATE 1

[Drawings based upon microphotographs of films stained with eosin and methylene blue after fixation by formaldehyde vapour.]

FIG. 1. Case of leukanaemia, Mar. 24, 1907.

Red corpuscles = 1,540,000 per c.mm.
 Leucocytes = 1,800 „

FIG. 2. Case of leukanaemia, May 10, 1907.

Red corpuscles = 2,800,000 per c.mm.
 Leucocytes = 34,000 „

and of the leucocytes 93 % were lymphocytes (40.9 % small, 52.1 % large).

FIG. 3. Case of acute leukaemia.

Red corpuscles = 1,900,000 per c.mm.
 Leucocytes = 104,600 „

and of the leucocytes 99 % were lymphocytes (17 % small, 82 % large).

FIG. 4. Case of 'splenomedullary' leukaemia with apparent change of type to lymphatic: blood in later stage.

Red corpuscles = 1,820,000 per c.mm.
 Leucocytes = 42,200 „

and of the leucocytes 82.8 % were lymphocytes (37.4 % small, 45.4 % large).

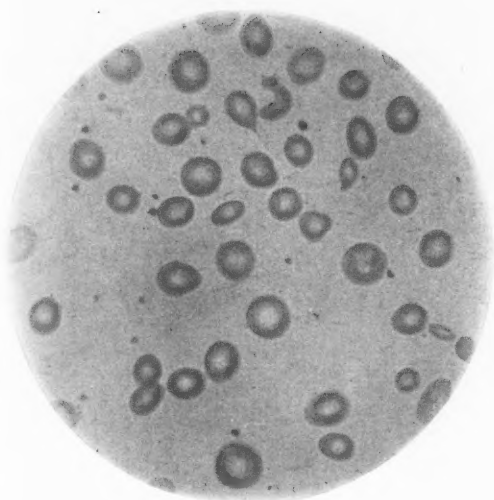


Fig. 1.

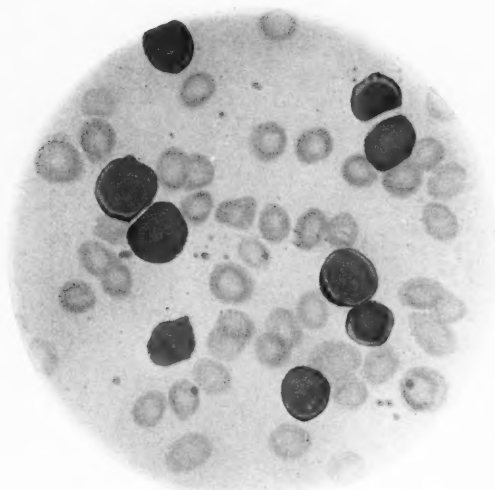


Fig. 2.

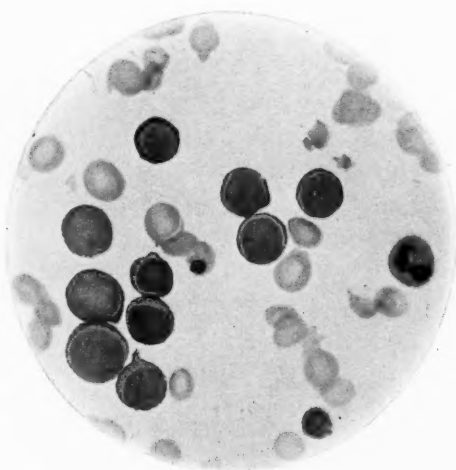


Fig. 3.

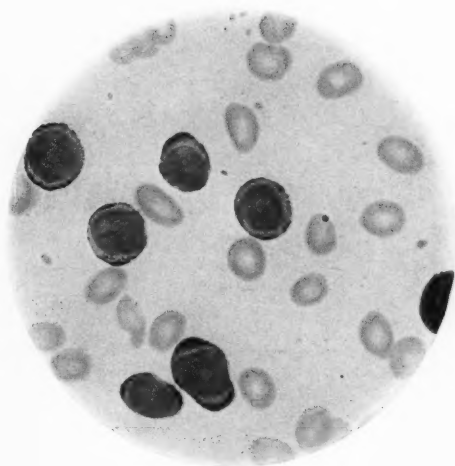


Fig. 4.

A CONTRIBUTION TO THE STUDY OF RHEUMATISM,
WITH NOTES ON THE AFTER HISTORY OF 25 CASES
OF 'SCARLATINAL RHEUMATISM'

By F. J. POYNTON

THE study of 'Rheumatism' is full of problems of the greatest interest, and those who once plunge into its depths find paths leading in so many directions that there is great difficulty in keeping any certain course. For this reason, before introducing this small contribution to the main subject, I mention some of the difficulties that have struck me as especially noteworthy at the present time. The first one is the realization of the logical outcome of the conception of acute rheumatism as an infective disease, of the streptococcal type. This difficulty can be illustrated from one of the most important of rheumatic lesions—arthritis. Not only has this symptom been frequently pushed into far too great prominence, but certain of the phases have been, I believe, unduly emphasized. The writings of many distinguished physicians have now placed rheumatic arthritis in its correct perspective, and I need hardly mention that it is a symptom which rises in importance as adult life is reached, in childhood sinking into comparative insignificance. But there is still, I think, too much emphasis laid upon the transient character of rheumatic arthritis, and the statement that suppuration does not occur in acute rheumatism is made in my opinion with more confidence than facts would justify. One key to the study of rheumatic processes must be an examination of the exudations and tissues, and I would ask if any one could at the present time say with confidence that their *gross* characters are peculiar? If the inflammation is very acute we find blood-stained exudations; if less acute, turbid; if subacute and severe, fibrino-plastic; if subacute and more severe, there will be many polymorpho-nuclear leucocytes in the fluid. In other words, we find the exudations varying with the virulence and duration of the process and having much the same *gross* characters as other inflammatory exudations. Surely it would be a strange occurrence if rheumatic suppuration did not occur occasionally, and it would prove a remarkable exception to the other infective processes which are akin. The experience of pneumococcal infection warns us also against any hasty conclusions as to suppuration, for suppurative lesions of that nature are now thoroughly recognized. I do not mean to imply that when suppuration occurs in rheumatism that it may not be in some cases due to a mixed infection, or, on the other hand, that when it occurs without secondary infection that there results a 'pyaemia', using the term in its loose everyday sense, but I believe that there is a *true rheumatic*

suppuration. This event is certainly not so frequent as in other allied infections, and when it occurs it is apt, I think, to be dismissed under the general term 'septic'.

Still dealing with the question of transient arthritis I would next emphasize the occurrence of cases of acute rheumatic arthritis in which all the joints, except one or possibly two, react to salicylate treatment and the rebellious one drifts into a condition of rheumatoid arthritis. A chronic arthritis deformans too is not rare in association with mitral stenosis, and I would venture to assert that there are cases of subacute rheumatism in which no two observers would agree whether the arthritis was rheumatic or rheumatoid. These latter cases occur most frequently in adolescent males and females, in whom acute rheumatism has produced profound anaemia. In such cases all such distinctions as implication of small joints, symmetry, and severe muscular wasting fail us: even tachycardia, so frequent in rheumatoid arthritis, cannot be denied as an event in acute rheumatism, for in chorea it may be persistent and there is a definite rheumatic affection of the heart in which irritability of action and not valvular disease is a feature, a point which has been carefully worked at and written upon by Dr. Carey Coombs in a recent number of this Journal.

Rheumatic arthritis in my opinion is neither from clinical experience nor from scientific reasoning invariably a transient condition, and if we turn to experiment we find that the rheumatic organism may produce acute arthritis, periarticular arthritis, osteo-arthritis, and even a non-articular osteo-arthritis, and these different results would appear to depend much upon the virulence and duration of the infection. Different though these lesions may seem when they occur in man, it may well be asked if the difference is greater than that between acute tuberculous arthritis and tuberculous osteo-arthritis?

It is not to be supposed that all subacute and chronic non-suppurative arthritic lesions are to be considered rheumatic, that would be to go far beyond facts, clinical observation, and legitimate reasoning; but for all the cogent reasons given above I hold that too much stress in 'rheumatism' is laid upon the phase of an arthritis as an evidence of a particular disease.

Nor is this a matter of scientific interest alone, it is one now of great practical moment, because there is a strong feeling that salicylate of soda is a specific for true rheumatism, and the inference is frequently drawn that when an arthritis does not react promptly to this treatment it is a proof that the condition is not rheumatic. Though open to conviction I doubt this and think there is a great danger of arguing in a circle if we accept it.

The arguments used for arthritis are applicable also, I believe, to other rheumatic lesions: thus endocarditis may be 'Simple', as in the usual form of mitral regurgitation, or 'Rheumatoid', as in mitral stenosis, or 'Rheumatic Suppurative', as in malignant rheumatic endocarditis. Pericarditis may be 'Simple' or 'Rheumatoid' when there is much thickening and subacute virulence, or lastly it may be 'Malignant', as in the most severe cases.

I may then once more repeat that if we accept acute rheumatism as a form

of streptococcal or diplococcal infection, we must be prepared to find many different phases and to admit that it may be modified by attendant circumstances just as, for example, pneumococcal infections are modified by influenzal epidemics.

The next difficulty in the study of 'rheumatism' is a more technical one. It is the difficulty that is found in isolating micrococci during life. This is again well exemplified by rheumatic arthritis, but it would be a mistake to think that this is peculiar to that condition, although this point has been greatly utilized by those who believe the cause of the disease is yet unknown. This particular point is one which, with Dr. Paine, I have been studying during the last five years, taking advantage of opportunities offered by surgeons who have opened or explored joints of a doubtful nature. It would be beside the purpose to enter here into the details, but we can make the general statement that smouldering forms of arthritis of many different kinds seldom yield satisfactory cultures, and in order to satisfy oneself as to the presence or absence of bacteria, it is necessary to examine many films from the exudations and each film very minutely. The reaction of human joints to bacterial infection is exceedingly vigorous, and in animals also there may be the same phenomenon of sterile cultures in arthritis, although there has been an intravenous injection of bacteria undertaken to produce this arthritis.

In spite of the fact that there is so much difficulty in isolating bacteria from 'rheumatic' joints, the more experience one has of the contents of such the more the conviction grows that the processes are bacterial, and failure does not imply that investigation is on the wrong track, but only that it is a difficult one.

Closely allied to this problem of the isolation of micrococci is that of gauging the relative importance of the bacteria themselves and the toxins they produce in acute rheumatism. It is possible that the bacteria produce toxins which have an effect quite out of proportion to the number of micrococci required to manufacture them, and further that the injury produced may depend greatly on the condition of the human tissues.

The next difficulty is one which needs very careful handling at the present time, because it depends upon the acceptance of the diplococcus of acute rheumatism. If this be accepted then we must, I think, be prepared to find that there are (to use a bacteriologist's expression) different 'strains'. It is an experience met with in dealing with such other micrococci as pneumococci and meningococci, and is for this reason to be expected with the micrococcus of rheumatism. It is this variability in the behaviour of bacteria in pathological conditions which leads one to write with such caution in the use of the word 'specific', either as applied to an infective agent or to a chemical remedy.

It seems probable that there is a large field open for investigation on the subject of the variability of the micrococcus rheumaticus, but at present there is great danger that we may find ourselves explaining away difficulties by making assumptions about different 'strains' before there is a general agreement upon the existence of such a micrococcus at all.

The next problem, one of the greatest and most pressing, is the complexity of the streptococcal group. It is difficult not to feel distrust of all methods of separation of the group which depends on laboratory tests on media of a nature not akin to the human tissues, for under such altered circumstances it is more than likely that the essential characters of such a variable group as this will be altered and a classification made on these lines may become practically useless, if not misleading. I would once more strongly protest against such a term as streptococcus 'faecalis' or 'salivarius'. Is it likely, I ask, that the faeces or saliva would breed a peculiar streptococcus? Are they media constant in composition, or can it be that such streptococci arise *de novo* in these media?

If we accept acute rheumatism as an infection, I cannot agree with the statement that is sometimes made that there is no such thing as a true chronic rheumatism. The difficulty of combating this has been increased by the use of the term 'fibrositis'. We now hear of a condition described as a 'fibrositis' as if this were in itself a disease. A moment's thought should convince us that a chronic inflammation of fasciae may own many causes. It is indeed a mere symptom, though, as used now even by some authorities, fibrositis is rapidly becoming a cloak for ignorance, a mysterious name, which satisfies the uninquiring and tells us nothing. It may be gouty, influenzal, rheumatic, syphilitic, or what not, but once get this term fixed in medical terminology and there will be a repetition of the difficulties which have been encountered over the terms 'septic' and 'pus'. Why should not the infection of rheumatism linger in the tissues, as is the case with other infections, and produce a chronic condition? It is much more probable that such would be the case than that an infection such as this should only manifest acute and subacute characters. The clinical facts appear to me to support the existence of a true chronic rheumatism, but in our present state of knowledge, when it is difficult to prove the existence of an infection in acute rheumatism, how much more difficult must it be to prove conclusively the existence of a true chronic rheumatism!

In these introductory remarks I have endeavoured to point out my belief that our views upon acute rheumatism as an infection must not be too rigid, but must be tempered by our knowledge of the variability in character and course of other allied infections, and if we take this broad view of the subject it is interesting to consider the particular problem to which these clinical details are attached, that of acute rheumatism and scarlet fever. This is of special interest because of its comparative frequency in this country, and because we have on one hand the researches of Mervyn Gordon and others on the streptococcus that occurs in scarlet fever, and on the other the investigations that have been made upon the same family of bacteria in acute rheumatism uncomplicated by scarlet fever. Further, in both scarlet fever and rheumatism the importance of sore throat is generally recognized, and lastly, whatever the true explanation of scarlet fever itself may be, we may reasonably look upon it as likely to influence any concomitant rheumatic infection.

In looking through the first volumes of the post-mortem records of the

Hospital for Sick Children, Great Ormond Street, which date back some fifty years, it is interesting to find oneself in the days when cases of scarlet fever were admitted and were often extremely virulent. It would have been still more interesting if cultures had been made in those days from the fatal cases of pericarditis, for then any micrococcus which had been isolated might have been compared now with that which has been since isolated from uncomplicated rheumatic pericarditis. Fortunately, the researches of Gordon enable us to get a clear idea of the streptococcus which he isolated from cases of severe scarlet fever and which has some points of close resemblance to the rheumatic micrococcus.

Clinical investigation has proved the occurrence of multiple arthritis, chorea, nodules, heart disease, sore throat, purpura, erythemata, and psoriasis, in association with true rheumatism and scarlatinal rheumatism, and in this contribution I have since 1900 traced the after histories of 25 cases of rheumatism in childhood directly associated with scarlet fever. These children have come to me for symptoms of rheumatism, and, so far as I can observe, the clinical features are identical with those of acute rheumatism. One case was fatal (No. VI) from pericarditis, and Dr. Paine isolated a diplo-streptococcus, which, working along the lines we had pursued in other cases, showed the same characters as the diplococcus of rheumatism. It was minute, strongly acid producing, diplococcal in the fibrinous exudation, and on experiment caused multiple arthritis and heart disease in rabbits with no suppuration in the viscera. The virulence was soon lost, but the growth once established was persistent in subculture.

It will be seen from the recorded cases that the children who suffered from rheumatism during scarlet fever were liable to relapses in which multiple arthritis or chorea or morbus cordis might light up again, and several of these symptoms might appear together. The arthritis was benefited by salicylates, the chorea ran the same tedious course, the cardiac lesions were chiefly mitral and showed no peculiarities, except perhaps a greater tendency to tachycardia.

Scarlatinal rheumatism is well known to commence either soon after the initial sore throat or, as these cases show, in association with a secondary sore throat, and this reminds us that the portal of entrance of the rheumatic organism which has been the most certainly proved is the tonsils. It may be mentioned in passing that among the many cases of acute rheumatism in childhood, recorded in my hospital notebooks, I find that the two other acute infections from which parents have dated attacks of rheumatism in their children have been measles and diphtheria, and both these are associated with sore throats. These personal investigations have been made quite independently of the views of other observers, but when they are compared with the statements that have been made in the standard article on scarlet fever by Caiger in Allbutt and Rolleston's System of Medicine, it is apparent that he, writing from his aspect of scarlatinal rheumatism, approaches towards the same position as the one to which I incline. Thus he writes: 'There are good reasons why it should be regarded as pathologically akin to ordinary acute rheumatism, though differing

in certain respects. It is very prone to arise in persons who have been subject to attacks of acute rheumatism, although such subjects are in the minority. It shows, though in a less degree, the same tendency to move from joint to joint, and it is readily amenable in most instances to the action of salicylates. On the other hand, it is less severe than ordinary acute rheumatism, its natural bent being towards recovery: it is unattended with the acid perspirations and the creamy furred tongue so characteristic of that condition, and it is less prone to affect the tissues of the heart and pericardium. Moreover, the joints are more prone to take on a suppurative action leading to a condition of pyaemia than in ordinary rheumatism.'

Caiger is naturally presenting the subject of scarlatinal rheumatism from a somewhat different point of view, for he is writing of scarlet fever irrespective of the age of the patients, and from observations during the course of the exanthem. On the other hand, I am concerned only with children under twelve years of age who have recovered from the scarlet fever, and I have seen the rheumatism when uncomplicated by its presence. Yet both of us, in common with many others, are struck by the close resemblance of true and scarlatinal rheumatism, and *I believe that it is in many cases true acute rheumatism*. Later in his observations Caiger adds that scarlatinal rheumatism is far more common in adults than in children, and that the cardiac structures are rarely involved at the time, probably in less than 3 per cent. These observations, if it were not for the saving clause as to the relative frequency in adult life, would, I think, be strong evidence against the true rheumatic origin of scarlatinal rheumatism. The saving clause reminds us that valvular and pericarditic disease are less frequent in adult than in child life.

My cases show clearly enough that heart disease is a common event in childhood after scarlatinal rheumatism. Thus 16 out of 25 had obvious organic valvular disease, and several of the remainder had dilated hearts or suspiciously feeble first sounds. Sour sweats, we know, are not a feature of rheumatism in childhood.

I must next make a brief reference to a remarkable discussion on rheumatism and its allies in children, introduced by Barlow at the annual meeting of the British Medical Association held at Liverpool in 1883. This is to look back over a quarter of a century! On the subject of scarlatinal rheumatism Barlow thus sums up: 'It seems possible that there may be at least two different forms, but at all events with regard to many of the cases occurring during convalescence, and with regard to the mild relapsing cases occurring towards the end of the first week, we must consider that if not identical they are indistinguishable from true rheumatism.' Ashby, in the discussion, described two cases in which pus was found in the joints and strongly lent to the pyaemic nature of this complication. To quote his words: 'In the first place, there is the greater frequency of occurrence in some outbreaks than in others. Secondly, the regularity with which the joint affection supervenes at the end of the first week; thirdly, the severity of the scarlatinal symptoms and the lightness of the joint affection in

most cases, and the suppuration which took place in two of the cases; and lastly, the absence of serious heart affections.' We may well wonder if to-day we have advanced a single step from the position of 1883. I believe, however, that the bacteriological investigations on scarlet fever and acute rheumatism have really brought us a little nearer to the means of closer investigation, and to a more complete understanding of the problem.

I think the clinical and pathological facts in my series seem to point irresistibly to the occurrence of true acute rheumatism in scarlet fever, although there is the other problem to be borne in mind, the possibility that there may also be a form of rheumatism peculiar to scarlet fever. This I am not in a position to affirm or deny, but I feel that if it exists it has not yet been clearly delimited from the true rheumatism, and we must bear in mind the possibility of a modifying influence on true rheumatism due to the scarlatinal poisoning. The bacteriological problem is a most difficult one, and it would be a great assistance if a careful investigation could be made by an independent observer of the micrococcus isolated by Gordon from scarlet fever and that obtained by Dr. Paine, myself, and others from acute rheumatism. I use the term 'independent' because it has repeatedly struck me that laboratory investigations on the streptococci are carried on by different methods, along different lines and with different standards by the various workers, and each one has a tendency to lay stress on some particular test or tests which he considers more or less specific. Vernon Shaw was able to prove to his satisfaction by the tests that he applied that the micrococci described by Wassermann, Paine, and Walker were identical. If some one working with virulent streptococci from scarlet fever of Gordon's type and virulent streptococci of the rheumatic type could make an unbiased comparison of them, it seems probable that we should gain another step in the study of rheumatism. That they are closely allied the researches of Gordon, Andrewes, Horder, Paine, Walker, and Beattie have already shown. What are their specific differences when studied together especially by experiment, and of what value are these specific differences, are what one would like to know.

Case I. Sept. 13, 1900. R. C. Female, aged 9. When six years old in 1897 she had an attack of scarlet fever followed in the fifth week by 'rheumatism' (viz. arthritis), which kept her in bed for some weeks. This child was brought to me in 1900 for a first attack of chorea with a dilated heart. In 1901 she was again brought to me for chorea. In 1902 for pleurodynia and endocarditis. In 1904 she had well-marked double mitral disease.

Summary. 'Scarlatinal rheumatism,' chorea, pleurodynia, morbus cordis; relapsing type.

Case II. Oct. 27, 1900. W. W. Female, aged $7\frac{2}{3}$. Scarlet fever in December, 1899. Not well since, but subject to sore throats and pains in the muscles. One sister had had rheumatic fever, another 'muscular rheumatism'. Sept. 1900, severe rheumatic arthritis. Oct. 1900, chorea, in hospital for seventeen weeks. March, 1901, chronic rheumatism and chorea still continue; evidence of early mitral stenosis now apparent.

Summary. Never well since scarlet fever; sore throats; arthritis; chorea; morbus cordis.

Case III. M. K. Female, aged 6. April 15, 1902. This patient was in a fever hospital suffering from scarlet fever and 'rheumatism' for thirteen weeks. Three days after leaving hospital she relapsed with pain in her left side and dyspnoea. She had never had rheumatism before, but her mother had suffered from rheumatic fever when twelve years of age, and an elder brother also suffered from rheumatism. She was exceedingly anaemic and orthopnoeic, with a temperature of 104° F., pulse of 144 and respiration 68 to the minute. Pericardial and pleuropericardial friction were present and also extensive endocarditis. Death occurred in seven days.

The necropsy showed a turbid greenish-yellow fluid with plastic exudations in the pericardial cavity. Early vegetations were present on the mitral tricuspid and aortic valves. Renal disease was present, and a small white infarct was also found in each kidney. A minute diplo-streptococcus, obeying the cultural and morphological characters of the rheumatic diplococcus, was isolated from the pericardial exudation by Dr. Paine. This produced arthritis, pericarditis, and endocarditis on intravenous injection into rabbits.

This was a case of particular interest because there was both a definite history of scarlet fever and a strong rheumatic family history. The micrococcus resembled the rheumatic diplococcus in essential characters, and the post-mortem evidence showed a condition quite indistinguishable from that found in virulent rheumatism.

Summary. Scarlet fever; 'rheumatism'; virulent and fatal pericarditis. *Necropsy.* Diplo-streptococcus in pericardial exudate produced multiple arthritis, pericarditis, and endocarditis on intravenous injection into rabbits.

Case IV. E. A. Female, aged 7½. June 18, 1902. When four years old had a severe attack of scarlet fever, immediately after which she complained of pain in her knee-joints, but recovered from this entirely. The following year she again had pain in her knee-joints with effusion which lasted for six months. The effusion appeared first in the left knee, then later in the right, and then again in the left. Since this second illness she had never been well. There was no personal history of rheumatic fever and no immediate family history, but her maternal grandfather suffered from rheumatic fever.

This child had great swelling of both knee-joints with much pain and muscular wasting. The left hip-joint was also painful. There was tachycardia, but no valvular disease. One enlarged lymphatic gland was felt in the right groin. The spleen was not enlarged. I explored the left knee-joint, obtaining a quantity of clear effusion, containing a few polymorphonuclear leucocytes, but no micrococci, and all cultures were sterile.

Salicylate treatment was ineffectual, and in September the condition was still most intractable, and although her general health was improved, both knee-joints presented the appearance of 'rheumatoid arthritis'. Most unfortunately I lost sight of her after September and must be accordingly content to record her case as one of rheumatoid type of obscure nature following scarlet fever.

Summary. Scarlet fever; 'rheumatism'; chronic relapsing arthritis of the rheumatoid type; tachycardia; cultures from arthritic exudation negative.

Case V. A. S. Female, aged 10. November 26, 1902. At five years of age was thirteen weeks in a fever hospital suffering from scarlet fever followed by chorea. Three years later was admitted to a London hospital for 'rheumatism in her joints'. Following the scarlet fever psoriasis developed and relapses occurred each year (five times) accompanied by pains in her limbs. She came under my observation for a second attack of chorea together with psoriasis.

Her heart was dilated and there was an occasional soft mitral murmur. This attack of chorea ran the usual course.

Summary. Scarlet fever; chorea (two attacks); arthritis; psoriasis (five attacks).

Case VI. C. W. Female, age not stated. March 7, 1903. Six months previously had an attack of scarlet fever followed by 'rheumatism'. During the scarlet fever her throat was very inflamed. This child had recovered from the arthritis, but was brought to me six months later for a severe attack of chorea, accompanied by dilatation of the heart and arthritic pains.

Summary. Scarlet fever; 'rheumatism'; chorea; arthritic pains; cardiac dilatation.

Case VII. W. S. Male, aged 6. Oct. 1903. In June, 1903, was ill for two months with scarlet fever. Three weeks later developed a sore throat followed by rheumatism for which he was detained five weeks in a London general hospital. In September, a week after leaving, he developed erythema multiforme, a sore throat, and shortness of breath. I found him suffering from severe mitral disease and bronchitis, and so far as I could ascertain this heart disease showed no characters by which it could be distinguished from ordinary rheumatic heart disease.

This case may be looked upon as an example of acute rheumatism which chanced to happen after an attack of scarlet fever, but the sequence of events is so close as to make it worthy of record when considering the wider question: What is scarlatinal rheumatism?

Case VIII. V. W. Female, aged 6. November 4, 1903. This child had an attack of scarlet fever at two years (in 1899), and ever since had been in poor health and suffered from shortness of breath owing to a damaged heart. She came under observation suffering from chorea with well-marked mitral disease and hypertrophy of the heart. The chorea was chiefly on the right side with much speech defect. In Jan. 1904 she had recovered from the chorea, but remained in the same condition as regards her heart.

Summary. Scarlet fever; morbus cordis; chorea.

Case IX. G. F. Male, aged 10. August 10, 1904. Scarlet fever at the age of 7 and at that time arthritis of the ankle-joints. At the age of 9 multiple rheumatic arthritis with heart disease. Brought to me in 1904 for a third attack of arthritis with tachycardia and a cardiac murmur. This boy improved under salicylate treatment. In April, 1905, he again relapsed with arthritis and cardiac disease.

Summary. Scarlet fever; arthritis (repeated); tachycardia; morbus cordis.

Case X. W. H. Male, aged 10. April 1, 1905. Quite well until scarlet fever at the age of 6 years in 1901; he was then in a fever hospital for three months suffering from 'rheumatism'. On returning home he developed chorea. This boy came to me suffering from a second attack of chorea with well-marked mitral disease, the condition being, so far as I could determine, indistinguishable from the chorea and morbus cordis of acute rheumatism.

Summary. Scarlet fever; arthritis; chorea (two attacks); morbus cordis.

Case XI. A. A. Female, aged 9. April 8, 1905. The mother of this child suffered from chronic rheumatism, and the patient herself, three months before coming under observation, suffered from an attack of multiple arthritis in the fourth week of scarlet fever. She was brought to me for rheumatism in the

limbs, dilatation of the heart, and slight chorea. Her illness ran an ordinary course.

Summary. Scarlet fever; arthritis; chorea; cardiac dilatation.

Case XII. M. O. Female, aged 9 $\frac{4}{12}$. May 15, 1905. This case presents the relation of scarlet fever and rheumatism from a somewhat different point of view. The patient had suffered from rheumatic fever when six years of age, and two years later from an attack of scarlet fever in which occurred multiple arthritis, affecting the wrists and knees. She came to me about eighteen months later with chorea and well-marked mitral disease. Her illness showed no unusual features. This case, as do several others in this series, exemplified the point that Caiger emphasizes in his article on scarlet fever in Allbutt and Rolleston's System of Medicine, i.e. the occurrence of scarlatinal rheumatism in those who are rheumatic in constitution.

Summary. Acute rheumatism; later scarlet fever and arthritis; later chorea and morbus cordis.

Case XIII. W. H. Male, aged 10. June 17, 1905. Four years before coming under my observation in 1901, he had an attack of scarlet fever followed at once by chorea. There was no family history of rheumatism. This boy had come to the hospital for an attack of rheumatism of three months' duration, commencing with arthritis and chorea. He had well-marked mitral disease with considerable dilatation. The condition was characteristic of ordinary acute rheumatism and recovered in the usual imperfect manner. In Nov. 1906 he suffered from epistaxis and again came back to me with a dilated heart, oedema, and severe mitral disease.

Summary. Scarlet fever; chorea (two attacks); arthritis; morbus cordis.

Case XIV. F. S. Female, aged 11 $\frac{1}{2}$. Oct. 28, 1905. Three years before (in 1902) she had an attack of scarlet fever followed by chorea three months later. During the scarlet fever there was 'rheumatism' in the joints. A year later there was a second attack of chorea. This patient came to me with a history of pains in the ankles and knees of 14 days' duration with mitral disease and violent chorea which ran a protracted course.

Summary. Scarlet fever; arthritis; chorea (three attacks); morbus cordis.

Case XV. K. R. Female, aged 7 $\frac{4}{12}$. Feb. 1906. This case is of interest for its bearing upon the rheumatism of scarlet fever. Her sister was suffering from rheumatic heart disease and chorea. The child herself had suffered from scarlet fever with severe angina, and had left the hospital three weeks. During those three weeks she was noticed to be exceedingly nervous and could not be left alone at night. She also complained of headaches. Then she became fidgety and came to the hospital with obvious chorea and cardiac dilatation. The chorea became severe, but she eventually recovered with apparently no permanent cardiac lesion. In Jan. 1908 she again came under me with a relapse of chorea associated with a sore throat.

Summary. Scarlet fever; chorea (two attacks); cardiac dilatation.

Case XVI. M. W. Female, aged 6. Oct. 27, 1905. This case again illustrates the close association of acute rheumatism and scarlet fever. The mother of the child suffered from 'rheumatism' and the patient in April, 1908, was nine weeks in a fever hospital suffering from scarlet fever, during which illness she developed multiple arthritis. Immediately on her return home she developed chorea. The patient came to me for shortness of breath and pain in the chest, and I found a characteristic early mitral lesion.

Summary. Scarlet fever; arthritis; chorea; morbus cordis.

Case XVII. B. C. Male, aged 7. Nov. 10, 1906. Two years before had an attack of scarlet fever with nephritis, and heart disease. He came to me suffering from a double mitral lesion with general cardiac enlargement and no renal affection.

It is not unreasonable to suggest the cardiac lesion was rheumatic, and possibly also the nephritis. It can be safely asserted that the condition of the heart did not resemble that which we usually recognize as a sequela of chronic renal disease in childhood. The high pulse tension, slightly thickened vessels, and hypertrophied left ventricle of such cases were not present, but there was a condition resembling the usual double mitral disease of acute rheumatism.

Summary. Scarlet fever; mitral disease; nephritis.

Case XVIII. L. M. Female, aged 8. June 12, 1907. The mother of the patient had suffered from rheumatic fever. The child herself had an attack of scarlet fever in February, 1907, and at the end of March developed chorea, for which she came to the hospital. Her recovery was good and without an apparent cardiac lesion.

Summary. Scarlet fever; chorea.

Case XIX. E. N., aged 7. February 22, 1908. When five years old had an attack of scarlet fever with nephritis and arthritis in the hands. Since that time has had rheumatic pains. Brought to me with morbus cordis. The heart was enlarged; there were a systolic mitral and a slight presystolic murmur.

Summary. Scarlet fever; arthritis; nephritis; morbus cordis.

Case XX. G. B. Male, aged 10½. April, 1908. The maternal uncle of the patient had suffered from rheumatic fever; his mother from 'rheumatics'. This child had an attack of scarlet fever in September, 1907, and had a relapse of sore throat followed by rheumatism in the joints, hands, wrists, and elbows being affected. In November, after recovery from the 'rheumatism', he developed chorea. Brought to me April 10, 1908, for a relapse of chorea.

Summary. Scarlet fever; arthritis; chorea (two attacks).

Case XXI. L. T. Female, aged 10. April 15, 1908. Some years previously had an attack of scarlet fever, followed at once by rheumatism in the joints. Since that time short of breath and subject to fainting attacks. This case was of interest, because there was persistent tachycardia (pulse 120), some general enlargement of the heart, and a faint mitral murmur. The urine was not albuminous. It appeared to be a case in which myocardial disease was the prominent feature, and I think the balance of evidence favoured the view that it was rheumatic in nature.

Summary. Scarlet fever; arthritis; morbus cordis.

Case XXII. W. P. Male, aged 6½. August 8, 1908. Scarlet fever a month ago. Brought for a sore throat. Anaemia; abdominal pain and pains in the wrist. Examination showed active heart disease with a temperature of 101.4°. This case ran a very severe protracted course, lying for many weeks in the hospital with active heart disease. In December, 1908, shortly after leaving the convalescent home, he returned to me very ill with a greatly damaged heart, rheumatic nodules over both elbows, and vague muscular and articular pains.

This case can perhaps hardly be claimed as an example of 'scarlatinal rheumatism', but rather as one of malignant rheumatism following scarlet fever. It is, I think, worth recording in the series, because though a month elapsed after the scarlet fever before the boy was brought to me, I am quite sure that the

condition had been in existence for some days, and possibly a week or more, which would date its onset very close to the fever.

Summary. Scarlet fever; morbus cordis; arthritic pains; anaemia; nodules.

Case XXIII. W. K. Female, aged 7. September 19, 1908. Scarlet fever and rheumatism in May, 1908. In September a return of the pains in the limbs with fever and sore throat. Early mitral disease. Her mother had suffered from rheumatic fever.

Summary. Scarlet fever and 'rheumatism'. Later, sore throat, rheumatic pains; morbus cordis.

Case XXIV. C. C. Female, aged 8. September 19, 1908. This child had previously been under my care, suffering from rheumatic morbus cordis. She now developed scarlet fever, and in October, immediately after the attack of fever was over, she became choreic.

Summary. Rheumatic fever; morbus cordis; scarlet fever; chorea.

Case XXV. C. T. Male, aged 9. November 11, 1908. Ten weeks before coming under observation had suffered from scarlet fever, during which there were rheumatic pains. Immediately on leaving he was noted to begin twitching. There was obvious chorea, anaemia, albuminuria, but no obvious cardiac murmur. His father suffered from rheumatism.

Summary. Scarlet fever; chorea; albuminuria.

An interesting point becomes apparent from a study of this series, viz. that one symptom of rheumatism may be noted while a child is in a fever hospital, which may quiet down under treatment. When, however, the child leaves there frequently appears within a month from departure another symptom of rheumatism (chorea in particular), showing that the disease was only apparently cured in the fever hospital. This has important bearing upon the ultimate prognosis of scarlatinal rheumatism.

ON LYMPHOCYTOSIS OF THE CEREBRO-SPINAL FLUID IN RELATION TO TABES

BY JUDSON S. BURY AND ALBERT RAMSBOTTOM

A causal relationship between syphilis and tabes and between syphilis and general paralysis of the insane is now admitted by the large majority of neuro-pathologists. The actual frequency of antecedent syphilitic infection in the history of the tabetic or the general paralytic has been variously stated by different observers, who have collected large numbers of cases, as to be from 70 to 90 per cent. By most authorities it is agreed that in about 10 per cent. of the cases syphilis cannot be proved or even suspected. Other causes, as injury, overstrain, cold, and wet, have been adduced to account for this small proportion of cases.

That these or other causes must play a part in determining the incidence of the syphilitic virus on the brain or the spinal cord, or on both, is suggested by the small percentage (1 to 5) of persons who have contracted syphilis, who subsequently suffer from tabes or general paralysis. A few authorities, however, as Professor Ferrier and Dr. Mott, do not believe that these diseases can develop apart from previous syphilitic infection, and go so far as to say 'no syphilis, no tabes'.

Obviously it is of great practical importance to determine whether syphilis is or is not absolutely necessary for the production of tabes and general paralysis. The statistical method having failed to decide this question, we must seek for some other method by means of which it may be possible to determine with certainty whether a person suffering from either of these diseases has had syphilis or not.

Quite recently some new tests, as Wassermann's and Curioni's reactions, have afforded help in this direction. Of these tests we have had no experience. But by means of an older method, namely, that of lumbar puncture, we have endeavoured to determine, first, if lymphocytosis of the cerebro-spinal fluid is a constant phenomenon in tabes and general paralysis, and secondly, if the degree of lymphocytosis in cases of tabes and general paralysis with undoubted evidence of antecedent syphilis is different from that found in cases where such evidence is wanting.

We were particularly induced to undertake the investigation from the consideration of an interesting case of tabes in a young unmarried woman. This patient, at the age of 22, began to suffer from weakness and darting pains

in the legs; a few months later from neuralgic pains in the right arm. A year later she came into the Manchester Royal Infirmary, and presented the following signs of tabes: slight ataxia, absent knee-jerk, unequal pupils which showed no reaction to light or accommodation, and slight anaesthesia of the hands, the right foot, and the right cheek. In this case we felt pretty confident on general grounds that antecedent syphilis was unlikely. The cerebro-spinal fluid was examined and found to be normal; there was no lymphocytosis.

We then decided to make a systematic examination of the fluid in all cases that came under our notice and to adopt a uniform method. In each case after the needle had been introduced, a few drops of cerebro-spinal fluid were allowed to escape in order to avoid any possible contamination with blood. About 6 c.c. of the fluid were then collected. This was well shaken and then 5 c.c. were measured and centrifugalized for five minutes. The superjacent fluid was removed by siphonage, and from the whole of the deposit a film was prepared and stained. The number of lymphocytes contained in five consecutive microscopic fields, using the $\frac{1}{4}$ objective and the No. 4 eyepiece, was counted. The first field counted was the one which, from a survey of the whole film, appeared to contain the largest number of lymphocytes.

A number of observations was first made upon the cerebro-spinal fluid of patients suffering from non-syphilitic nervous affections, and contrasted with those made from cases of cerebro-spinal syphilis. In the non-syphilitic cases, which comprised two of cerebral tumour, three of neurasthenia, two of Menière's disease, and one case each of epilepsy, progressive muscular atrophy, and bulbar paralysis, the degree of lymphocytosis was found to vary from 0.5 to 1.5 lymphocytes per field; whilst six cases of cerebro-spinal syphilis gave the following results: 7.6, 8.4, 10, 14.7, 18, and 495.6 lymphocytes per field.

With regard to tabes and general paralysis, we have examined thirty-four cases and in twenty-nine of them we found a decided lymphocytosis. In each of the five cases without lymphocytosis no history of syphilis could be obtained or reasonably assumed. It is also to be noted that in no case, where there was a history of syphilis, was lymphocytosis absent. On the other hand, two patients, who denied syphilitic infection, presented lymphocytosis of the cerebro-spinal fluid.

To sum up the results of this investigation:—lymphocytosis was found in about 85 per cent. of cases of tabes and general paralysis. In the remaining 15 per cent. there was no lymphocytosis, and no evidence of antecedent syphilis could be obtained.

We therefore feel justified in concluding (1) that lymphocytosis is not, as Purves Stewart and others have asserted, a constant phenomenon in tabes and general paralysis, and (2) that although syphilis may play an important part in the production of these diseases, it is not an essential factor.

TABLE OF RESULTS

Tabes Dorsalis

NAME	AGE	HISTORY OF SYPHILIS	AGE WHEN SYPHILIS WAS ACQUIRED	AGE WHEN SYMPTOMS FIRST NOTICED	LYMPHOCYTES PER FIELD
Jas. W.	42	acknowledged	22	38	28.2
Jos. S.	39	acknowledged	19	35	59.8
Jas. G.	40	acknowledged	20	36	20
Elijah C.	58	acknowledged	26	54	20.2
Chas. G.	52	acknowledged	28	48	20.6
Ellen R.	30	—	—	28	53.6
Sam. R.	44	denied	—	39	1
Edward O'B.	32	acknowledged	22	30	92.8
John S.	57	denied	—	54	8
Jas. H.	71	acknowledged	27	51	15
Michael B.	49	acknowledged	19	44	70.4
John K.	44	acknowledged	21	39	25.6
John C.	46	acknowledged	24	41	12
Chas. G.	68	denied	—	67½	1
Sarah R.	47	—	—	46	14
George C.	31	acknowledged	22	28	34.6
Esther T.	47	—	—	43	63.8
Frances W.	53	—	—	51	13.2
John T.	40	acknowledged	18	35	17
Jas. R.	45	acknowledged	19	45	56.6
Jas. R.	43	acknowledged	18	41	18
Robert S.	39	acknowledged	22	30	36
Nellie N.	37	—	—	37	24
Sam. M.	36	denied	—	22	0.8
Jas. T.	37	denied	—	36	0.4
Ada C.	39	—	—	32	42
George H.	37	denied	—	36	19

General Paralysis

NAME	AGE	HISTORY OF SYPHILIS	AGE WHEN SYPHILIS WAS ACQUIRED	AGE WHEN SYMPTOMS FIRST NOTICED	LYMPHOCYTES PER FIELD
Andrew S.	38	denied	—	37	1.6
Jas. W.	39	acknowledged	unknown	unknown	21
Andrew P.	43	acknowledged	unknown	unknown	29
John B.	38	acknowledged	unknown	unknown	38
Thos. D.	34	acknowledged	20	31	42.4
Arthur L.	37	acknowledged	21	36	19
Fred. W. B.	36	acknowledged	26	35	18

POLYCYSTIC DISEASE OF THE KIDNEYS

By CAREY COOMBS

A MAN of 30 was admitted to the Bristol General Hospital on March 24, 1908, under my colleague, Dr. Michell Clarke, who has kindly allowed me the use of the notes. He had been ill for three weeks with pain in the back, vomiting, bleeding from the mouth, nose, stomach, and rectum, and stupor succeeded by a condition of muttering delirium in which he was admitted. Soon after coming in, he became comatose and died. His teeth were caked with clot, and during his short stay in the ward blood was issuing from the rectum.

In the absence of the regular pathologist, I made the post-mortem examination. The submucous coat of the stomach and intestines was infiltrated throughout with blood which appeared to have come from hosts of capillary extravasations. The left kidney and ureter, also the left adrenal gland, were entirely wanting; there was not even a trace of an opening into the bladder on the left side. The right ureter was enlarged but not obstructed; the right kidney was the seat of a moderate degree of polycystic disease which spared a fair proportion of normal renal substance. There were a few small cysts in the liver.

This case provoked inquiry into the whole subject, especially in four directions. Such an inquiry seemed to be best conducted by an examination of all the available museum specimens. This examination has been made possible by the courtesy of the various authorities of most of the London museums as well as those in Bristol.

The submucous haemorrhages were certainly capillary and probably toxic. In three other cases there was a record of similar intestinal haemorrhages. One is irresistibly reminded of the purpura and haemorrhages from mucous membranes which occur in chronic nephritis, and especially in association with the contracted white kidney. The arterial haemorrhages due to high blood-pressure which occur in this latter disease sometimes complicate cases of polycystic kidney; reference will be made to this point later.

As an instance of conglomerate cystic disease of an unpaired kidney, this case is rare if not unique. This, of course, is no more than one example of the association of cystic kidney with definitely congenital defects, an association which has been used a good deal in support of the developmental theory of this disease. My inquiry has not thrown much light on this controversy as to the

origin of cystic disease of the kidney in adults. The facts unearthed may, however, be briefly written down for what they are worth.

In four cases (out of a total of fifty-eight specimens) there were other definitely developmental defects; all these occurred in infants born dead or dying soon after birth. In ten other cases there were cysts in the liver; one of these was a child dying at $8\frac{1}{2}$ weeks, another at 9 months; the other eight were adults. The naked-eye appearance of the infantile cystic kidney differs from that of the adult in the greater uniformity of size and precision of arrangement of the cysts in the former. This series of cases cannot be said to present any real evidence in support of the congenital theory, while a study of the ages at which death occurred distinctly militates against it. Eight cases (including still-births) ended at or before the age of $3\frac{1}{2}$ years; while of forty-five others in which the age is recorded, only three failed to reach the thirtieth year, and not one died before twenty. This leaves a wide gap very difficult to bridge over: the only connecting link is supplied by the occurrence of hepatic cysts in infantile as well as in adult cases.

This case brings into prominence the relation between the clinical phenomena of the last phase of cystic disease of the kidney and the degree to which the renal substance is destroyed. The disease was not so far advanced as in most museum specimens; yet the final symptoms were toxic and may be properly called uraemic, and the end came at an earlier age than is usual. An obvious explanation is that the disease, though moderate in degree, had destroyed the greater part of the patient's only kidney, reducing his renal tissue to the minimum compatible with life. Now it is of some importance to see whether this conception is applicable, not to this case only, but to cases of polycystic kidney as a general rule; whether there is any constant relation between the amount of healthy kidney substance and the onset of symptoms which may fairly be regarded as indications of systemic poisoning, such as are familiar in association with chronic nephritis.

The museum specimens to which clinical notes were attached were forty-four in number; twelve of these were examples of moderate, thirty-two of advanced cystic disease. Of the latter, eighteen, or more than half, had had fatal symptoms of uraemia, while among the twelve moderate cases there were only four such deaths. These four included the case described here, in which the disease, though moderate, was destroying the patient's only kidney; and another in which there was a moderately cystic kidney on one side and a contracted granular kidney on the other. In connexion with these observations another case¹ may be recalled: that of a man of 38, whose right kidney was removed for cystic enlargement on the supposition that the other kidney was healthy. Eight days after operation the urine became scanty, and headache with muscular twitchings set in, though previously there had been no such symptoms. At the autopsy the left kidney was found to be cystic also.

¹ Bristol General Hospital Museum, No. 945.

The fact that *this case was terminated by a syndrome in which symptoms of poisoning of the central nervous system predominated* is of interest. Apart from experiment, a simpler form of progressive destruction of the renal substance than that seen in polycystic disease can scarcely be imagined. It is not complicated by lesions in other organs; there is no infective factor to dispute with the renal inadequacy the authorship of toxic symptoms. What are the effects of this simple, gradual abolition of the renal functions upon the body as a whole? How do persons with polycystic kidneys die?

An analysis of the forty-four cases mentioned just now gives this result: that in twenty-two, or exactly half, the symptoms of the last phase were those of uraemia; in nine, death was due to cardio-vascular disease (cerebral haemorrhage five times, cardiac failure, hydropericardium, ascites, and rupture of a small aortic aneurism into the pericardial sac, once each), while thirteen died from accidents, intercurrent infections, or separate diseases. Several of this latter group must be looked upon as partly renal deaths: for example, in the museum of the University College Hospital is a specimen from a patient who died of pneumonia, but who had been previously diagnosed as a case of Bright's disease by Dr. Walshe. The symptoms included under the heading 'uraemia' correspond closely to the nervous syndrome most properly described by that title, a syndrome which is characterized by headache, vomiting, convulsions, and coma. I will illustrate this by a case in which I made the post-mortem examination. A man, aged 45, was admitted in May, 1906, to the Bristol General Hospital under my colleague, Mr. H. G. Kyle, whose notes are briefly reproduced here by his kind permission. He had had three epileptiform attacks in the eighteen months that preceded admission; in February, 1906, the abdomen became enlarged and painful, and vomiting began. These symptoms continued and increased in severity; haematuria occurred from time to time, he became thin and weak, and a few days before death the convulsive attacks recurred, with repeated vomiting, headache, weakness of the right arm, abnormally deep breathing, and stupor passing into coma, in which he died. Post mortem, we found both kidneys very large, and riddled with cysts, the largest of which were the size of a chestnut. Between these were the merest strands of renal substance, which, on microscopical examination, showed a structure surprisingly little altered from the normal. There was also an early general peritonitis, possibly due to infection from one of the renal cysts which contained pus and was covered over by the adherent great omentum.

Other symptoms besides those alluded to above as the cardinal features of true uraemia were wasting, anorexia, and urinous breath, each of which is several times mentioned; muscular cramps, weakness of one limb, numbness of one limb, and retinal haemorrhage. Oedema is mentioned six times; twice it is particularly described as general. These uraemic symptoms usually occurred for the first time a few months (at the most) before death; but one man was uraemic on and off for ten years before his death, and in another case where uraemia with oedema characterized the final stage of the case, similar symptoms had appeared

temporarily three years before. The urine is, as a rule, copious, of low specific gravity, with a trace of albumin and occasional bursts of haematuria.

Taking these uraemic cases with those in which death was due to circulatory lesions, a close analogy with the final phases of chronic nephritis, and especially of 'contracted white kidney', is at once seen. In both, the last phase is often one of toxæmia, in which nervous symptoms play the chief part; in both, there are changes in the circulatory apparatus attributable to a heightened arterial tension; in both, oedema occurs in a certain proportion of cases, but not constantly; in both, capillary haemorrhages under the skin and mucous membranes are sometimes seen. To these points of similarity may be added the liability of both diseases to be terminated by intercurrent infection.

Summary and Conclusions.

1. Toxic capillary haemorrhages sometimes occur in polycystic disease of the kidney.
2. A case is here recorded of polycystic disease in an unpaired kidney.
3. It has been shown that in polycystic disease of the kidneys, a simple but progressive form of renal dissolution, toxic symptoms appear when the available secreting tissue of the kidney has reached an irreducible minimum.
4. These toxic symptoms, taken with the effects of polycystic disease on the heart and blood-vessels, imitate very closely the analogous phenomena of chronic nephritis, and especially those of 'contracted white kidney'.
5. In each of these two diseases there is a steady wearing down of the renal substance which ends in uraemia with cardio-vascular changes. In obstructive suppression and total nephrectomy, uraemia (in the proper sense of the word) does not occur. This is probably due to the difference between the two types of disease in regard to the relation between the kidney and the circulation of blood through it. In polycystic disease and chronic nephritis, the renal cells, though progressively diseased, are still in active relation with the circulating fluids; in the other group, this relation has ceased to exist.

AN INVESTIGATION INTO THE HISTOLOGICAL CONDITION OF THE SUPRARENAL GLANDS IN CONDITIONS ASSOCIATED WITH A HIGH BLOOD PRESSURE

By AUSTIN PHILPOT

Introduction.

WHEN the important physiological discovery was made that the injection of suprarenal extract uniformly caused a rise in the blood pressure, and if long continued might lead to changes in the aorta (e.g. in the rabbit), it obviously suggested itself to pathologists to inquire whether the increased arterial tension met with in certain morbid states might be associated with definite changes in the suprarenal bodies. Vaquez having been the first to postulate an increase in function of these bodies in cases of chronic interstitial nephritis, Aubertin and Ambert, in 1904, examined the suprarenals of eight cases suffering from contracted granular kidneys with increased blood pressure, and found hyperplasia or adenomata of the cortex in seven of them. Out of nineteen cases without high blood pressure a similar condition was seen only once. In no case did the medulla show any signs of hypertrophy. They contended that the cortical hyperplasia was to be considered as a reactionary hypertrophy to meet the prolonged intoxication present in these cases of chronic interstitial nephritis and high blood pressure. Josué, Vidal, Ménétrier, and several others have found hyperplasia or adenomata of the cortex in cases of high blood pressure.

Changes in the medulla in similar cases have been described by Wiesel, Schnur, Parkinson, and others. Wiesel examined twenty-two cases of chronic interstitial nephritis with increased arterial tension and long-standing cardiac hypertrophy. In all of them he found a hyperplasia of the chromaffin substance in the suprarenal medulla, the solar plexus, and elsewhere in the body. He also found a hyperplasia of the chromaffin substance in a case of aortic insufficiency with cardiac hypertrophy. He concluded that cardiac hypertrophy was associated with hyperplasia of the chromaffin system. Parkinson examined fourteen cases of high blood pressure and found an increase of the chromaffin substance in all except three, in which a trace only was present. In thirty cases of low blood pressure the chromaffin was absent in twenty-two and present in eight. He concluded that in cases of high blood pressure the chromaffin substance was retained in the suprarenals, and in cases with a low blood pressure it was used up in an endeavour to keep the blood pressure up to the normal standard.

¹ Part of a thesis presented for the degree of D.M. in the University of Oxford.

[Q. J. M., Oct., 1909.]

Beaujard has attempted to reconcile these two divergent views by supposing that the cortex hypertrophies to provide an antitoxin to the toxin circulating in the blood in cases of chronic nephritis, and that the medulla hypertrophies and contains a larger amount of chromaffin substance in cases of high blood pressure with cardiac hypertrophy, where an increased secretion is necessary to give tone to the vessels already damaged by the strain put on them by the more forcible action of the heart.

The present inquiry was undertaken with a view of revising and supplementing the observations already made and in the hope that thereby more light might be thrown on an obscure and difficult problem. It resolved itself into an investigation into the histological structure of the suprarenals in cases in which there were definite clinical or pathological signs of a high blood pressure during life.

Method of investigation.

The suprarenal glands and the kidneys were removed from the body generally within twenty-four hours after death. In all cases the bodies had been placed in a freezing chamber soon after death until the post-mortem examination was made. The general naked-eye appearance of the organs was observed, and after clearing away the fatty covering they were weighed. Sections were also examined macroscopically. Portions were taken from each suprarenal gland and kidney and placed for twenty-four hours in Orth's fluid, a mixture made up of

Sodium sulphate	1 gramme
Potassium bichromate	2.5 grammes
Formalin 40 per cent.	10 c.c.
Water	100 c.c.

In some cases Kohn's mixture (90 parts of a 3 per cent. solution of potassium bichromate and 10 parts of a 40 per cent. solution of formalin) was used. Both mixtures gave similar results. Portions of kidney and suprarenal were then washed in running water for twenty-four hours, placed in a solution of gum for twenty-four hours, and cut on a freezing microtome. Sections were stained with Scharlach R. and mounted in Farrant's solution. Other portions were hardened and embedded in paraffin. Sections were cut on the microtome and stained with various solutions:—Haematoxylin and eosin, Van Gieson's, Weigert's elastic tissue stain and a solution of potassium bichromate and hydrochloric acid. One set of sections was stained with methyl violet.

Twenty-seven cases in all were examined. Of these nineteen were cases of chronic interstitial nephritis, three of hypertrophy of the left ventricle without chronic interstitial nephritis, and five cases of presumably low blood pressure.

Table of Results.

		BLOOD PRESSURE	WEIGHT OF SUPRARENALS	FAT IN CORTEX	SIZE OF MEDULLA	AMOUNT OF CHROMAFFIN SUBSTANCE
	act.					
First set: High tension cases.						
1. Chronic interstitial nephritis and arterio-sclerosis	45	184 mm. Hg.		marked	large	moderate
2. Chronic interstitial nephritis and fractured base	70			marked	large	increased
3. Chronic interstitial nephritis and senile gangrene	75			present	very large	increased
4. Chronic interstitial nephritis and subacute pleurisy	35	205	11.85 grammes	very marked	large	increased
5. Chronic interstitial nephritis	37	184	14.75	marked	large	increased
6. Chronic interstitial nephritis and uraemia	24		10.4	faint, marked in places	very large	moderate
7. Chronic interstitial nephritis	56			faint	very large	much increased
8. Chronic interstitial nephritis and symptomatic purpura	30		9.65	faint, marked in places	very large	much increased
9. Chronic interstitial nephritis and chronic pleurisy	57	170		very marked	fair	increased
10. Chronic interstitial nephritis and cardiac dilatation	43		13.6	present	fair	moderate
11. Chronic interstitial nephritis and tubercular laryngitis	39		15.45	very marked	very large	increased
12. Chronic interstitial nephritis and cerebral haemorrhage	16	145	6.0	marked	large	much increased
13. Chronic interstitial nephritis and uraemia	36	155		marked	large	increased
14. Chronic interstitial nephritis and abdominal aneurism	70		12.65	poor	very large	increased
15. Chronic interstitial nephritis and Stokes-Adams disease	35				large	increased
16. Chronic interstitial nephritis and ulcerative endocarditis	49	170	12.9	very marked	very large	much increased
17. Chronic interstitial and acute nephritis	32		9.15	present	very large	much increased
18. Aortic aneurysm and hypertrophy of the l. ventricle	51		9.5	present	large	moderate
19. Aortic disease and hypertrophy of the l. ventricle	46		22.6	very marked	very large	moderate
20. Cerebral haemorrhage and hypertrophy of the l. ventricle						
Second set: Low tension cases.						
21. Diabetes	37		8.0	present	small	present
22. Pernicious anaemia	42			faint	very small	trace
23. Laryngeal diphtheria	4				fair	present
24. Carcinoma of the pylorus	54		7.4	very marked	very small	trace
25. Carcinoma of the stomach	60		7.75	faint	very small	trace
Controls.						
26. Chronic interstitial nephritis and pericarditis	27			very marked	very large	much increased
27. Chronic interstitial nephritis and adenoma of the prostate	79		12.7	very marked	large	much increased

General appearance and structure of the suprarenals.

Fifteen out of the twenty-seven pairs of suprarenals were firm and well preserved; of the remaining twelve one gland was better preserved than the other, and as a rule the left one was larger and firmer than the right. In Case XXII the medulla of one suprarenal was very much disintegrated, the cortex remaining as a mere shell. When it was possible to remove both entire, the glands were freed from the surrounding fat and weighed. The weights varied from 6 to 22.6 grammes. Ten of the twenty-seven pairs showed cortical outgrowths (adenomata) on the surface. These varied from quite microscopical structures to the size of a pin's head. On naked-eye inspection the section of the suprarenal often appeared to be composed of three zones—a peripheral pale yellow part, a central light brown part, and an intermediate dark brown part. Under the microscope it was seen that the peripheral part was formed by the outer vacuolated part of the cortex, the dark brown by the non-vacuolated part of the cortex, and the central part by the medulla.

Histological examination.

A. Cortex. The connective-tissue capsule varied greatly in thickness. It was most marked in the small suprarenals of Cases XXI, XXIV, and XXV. In Case XIX prolongations of connective tissue were seen running down between the columns of the zona fasciculata. The zona glomerulosa was well stained and contained a small amount of fat in all the cases examined. The zona fasciculata varied greatly in staining properties—this depending on the amount of fat present. Where this was found in large quantities the cells of the zona fasciculata, treated with alcohol and haemalum, presented a spongy appearance. This was due to the presence of numerous vacuoles almost filling up the whole cell and leaving very little protoplasm to take up the stain. The nucleus, in most cases, was of normal appearance. Where, however, the vacuoles were very large it was flattened up against the side of the cell wall. In a few of the sections there were areas of vacuolated cortical cells without nuclei. In no case did the nuclei appear at all degenerated.

The zona reticularis was very well marked in some of the cases, especially in those which showed cardiac failure with congested organs. In these cases the medulla shared in the general vascularity. The brown cortical granules were present in most of the cases, forming a narrow zone at the junction of cortex and medulla. They were particularly well marked where there was much vascularity. In some cases they occupied the whole breadth of the reticular zone. In no case did these granules give the free-iron reaction.

Cortical adenomata were present in ten cases. Most of them were superficial and external to the connective-tissue capsule of the gland. Some were partly embedded in the cortex, and in one case a large adenoma projected above the surface of the gland and also encroached slightly on the medulla (Case XIV). The cells of these adenomata were usually made up of cells of the glomerular

and fasciculate zones, but in some cases pigmented cells of the reticular zone were also present. They contained a certain amount of fat in all cases.

The *cortical fat* varied greatly in amount. In the most marked cases it occupied the whole of the cortex, in less marked cases it occupied a central strip of the zona fasciculata or was faintly scattered throughout this zone. The zona glomerulosa never contained much fat. Fatty acid crystals were present in thirteen cases. They varied in proportion to the amount of fat present. In Case XX crystals were seen in the cortical cells lying in the medulla. In no case were they seen lying free in the medulla.²

B. *Medulla*. The medulla varied greatly in size. In some cases it occupied a mere strip between the two layers of the cortex. In others it was four to five times as broad as the cortex. Sometimes in the same case the medulla of one gland was much larger than that of the other. Fat was present in the medulla of all the cases examined. The fatty granules were many times smaller than those of the cortex. This was very noticeable where fatty cortical cells lay free in the middle of the medulla. Nerve ganglia were seen in the medulla of two cases (Nos. XVI and XXVI). The elastic tissue was well marked in every case. In nearly every case clumps of cortical cells, containing fat and pigment, were present in the medulla. In some cases they were connected with the zona reticularis, in others separated from it by medullary cells.

Clumps of round cells were occasionally seen near the central vessel of the medulla. The chromaffin stain was given by minute granules in the medulla in every case. The brown coloration of the medulla of the gum sections varied from a very light to a dark brown. In some cases it was present in patches in the medulla. In the paraffin sections stained with haemalum and eosin the granules were very hard to see, being masked by the general stain. When they were very abundant they were seen to be small dark brown granules. In no case was there any difficulty in distinguishing these granules from the larger, light brown granules of the cortical cells, which were seen in the medulla of most of the cases.

Comparison of the conditions found in the two sets of cases.

In every case in which the suprarenals were weighed, with the exception of Case XIII, a boy 16 years old, those of the first set weighed more than those of the second set. The average weight of the first set was 12.4 grammes, that of the second 7.7 grammes. The excessive weights of Cases XII and XX were probably due to the increased vascularity, that of Case XI to the lardaceous deposit. The first nine cases were not particularly vascular and the average weight of the four cases weighed was 11.86 grammes.

² Powell White examined the suprarenals of thirty cases, dying of various diseases and of all ages, and found these crystals present in every case. He also found them in the medulla of a child three weeks old. He states that they are a normal constituent of the suprarenal gland and are composed of cholesterol with lecithin or fatty acids.

Although these cases are very few in number, it is probably fair to assume that the suprarenals of cases with high tension weigh more than those with low tension. Apart from these weights the suprarenals of the high tension cases appeared to be much bigger and felt firmer than those of the low tension set. The cortex presented no distinctive characters in the two sets of cases. Hornowski and Nowicki examined the suprarenals of thirty-six cases of arterio-sclerosis and found an increase in size of the connective-tissue capsule with an obliteration of the zona glomerulosa in all. In the present investigations the thickness of the connective-tissue capsule appeared to vary with the size of the suprarenal gland. In the small suprarenals of Cases XXI, XXIV, and XXV it was very thick, and strands of connective tissue were seen running down between the columns of the zona fasciculata. In most of the suprarenals of the high tension set of cases the connective-tissue capsule was of normal thickness; in Case XIX, however, it appeared to be increased in size. In no case was the zona glomerulosa obliterated by the connective-tissue capsule.

Small adenomata were present in both sets of cases. They were seen in Cases XXIII, XXV of the low tension set, in Cases I, IV, VII, XIV, XV and XVI of the first set, and XXVI and XXVII of the controls. In no case was there a relative increase of the cortex, as described by Aubertin and Ambert. The amount of fat present in the cortex bore no relation to the amount of chromaffin substance present in the medulla. In the set of low tension cases it was poorly developed in three cases, but very marked in the fourth (Case XXIV). Experimenting on the guinea-pig, Elliott and Tuckett found that in cases of grave exhaustion the fat spread throughout the suprarenal cortex, taking the place of the brown granules of the zona reticularis. In Case XXIV, although there was a large amount of fat present, the pigment layer was fairly well marked. In the other three cases, all of which were cases of grave exhaustion, so far from the fat being increased in amount it was only present to a slight degree.

Small acicular crystals were present in the cortex of both sets of cases. The pigment granules of the zona reticularis varied in proportion with the vascularity of this zone and appeared to bear no relation to the blood pressure. The size of the medulla also varied. In the cases of the second set, with the exception of Case XXII, it was extremely small, occupying a mere strip between the two layers of cortex. These were all cases of chronic wasting diseases. Case XXII was one of a boy of four years old, who died of diphtheria after a three days' illness. In this case the medulla was of normal size. In the cases of the high tension set the medulla was enlarged in nearly every instance, in some cases being five times the width of the cortex. In only three of the cases was the medulla not increased above the normal size.

The chromaffin substance was present in both sets. In the low tension set only traces were seen. This diminution in the amount of chromaffin substance present in cases of wasting diseases agrees to a certain extent with Mott's results. He examined the suprarenals of seventy-one cases dying of various diseases at Claybury Asylum, and found that in cases of wasting disease no adrenalin could

be obtained from the glands. Elliott and Tuckett also found that under various conditions of ill health the chromaffin substance disappeared from the cells of the guinea-pig's medulla. In the high tension set the chromaffin substance was increased in every case except six, and in these there was a fair amount present.

Conclusions.

All the evidence obtained from a study of these cases points to the medulla as being the part of the suprarenal gland which is the seat of change in cases of high tension. There was no evidence to show that the cortex was affected in any way, either in the direction of increase of size or of histological structure. It has been shown that in cases of high tension, whether they are associated with interstitial nephritis or not, the medulla is enlarged in nearly every case. And besides this they nearly all present a definite increase in the quantity of the chromaffin substance, the active principle of the gland. In direct contrast to this is the condition found in the cases of exhausting diseases examined. Here in every case the gland itself was very small, the medulla was very narrow, and only traces of the chromaffin substance were present.

These results fit in very well with those obtained by Oliver and Schäfer and others, who from experiments on the physiological properties of the gland have shown that it is the medulla alone which produces the active principle.

These investigations tend to show that, besides the usual factors associated with or causing a high blood pressure, a condition of increased activity of the suprarenal glands, or hyperepinephrism, as it has been called, is very often, if not invariably present. The exact manner in which this arises must be left for future investigation.

I must express my thanks to Dr. Dudgeon for much kind advice, and also to those members of the Staff of St. Thomas's Hospital who have allowed me to refer to their cases.

DETAILS OF CASES.

Twenty-two cases with high blood pressure.

Case I. Chronic nephritis and arterio-sclerosis. G. G., male, aged 45. In hospital fifty-two days. On admission the patient was drowsy, but no muscular twitchings were observed. There was no oedema. The vessel walls were greatly thickened. His blood pressure measured between 174 and 194 mm. Hg. The urine contained albumin, between 0.68 and 1.75 grammes per litre. The urea measured about 5 grains to the ounce. He had albuminuric retinitis. Fourteen days before death he became paralysed down the right side and partly aphasic. There was no change in sensation.

Post mortem. There was a large haemorrhage in the left cerebral hemisphere, involving the posterior limb of the internal capsule. The heart was greatly hypertrophied. The aorta and other arteries of the body were rigidly thickened

with plates of atheroma. The kidney was small and typically granular. The suprarenals were firm and large. The heart weighed 22 oz.; the kidneys, 8½ oz.

Histological examination. The kidneys showed a great increase of interstitial connective tissue. The arteries were enormously thickened, the elastic tissue on either side of the media being greatly increased in size and amount.

The cortex of the suprarenals has a capsule of normal thickness. Several outgrowths of cortical cells were seen separated from the rest of the cortex by connective tissue. Some of the cells of these outgrowths were well stained, others were poorly stained and vacuolated. The zona fasciculata was poorly stained and vacuolated in places. The nuclei of these vacuolated cells presented a normal appearance; in places, however, they were absent. The pigment layer was well marked. The medulla was well developed. It contained several clumps of cortical cells, some in connexion with the rest of the cortex, others separated from it by medullary cells. They contained pigment and were evidently derived from the zona reticularis. The elastic tissue was increased in amount. The chromaffin reaction was well marked.

Case II. Fractured base and chronic interstitial nephritis. H. H., female, aged 20. In hospital twenty-four hours. On admission the patient was found to have a flaccid paralysis of the right arm and leg. She died without recovering consciousness.

Post mortem. There was a linear fracture of the skull in the right parietal region. The cerebral vessels were atheromatous. The kidneys were small. The capsules were adherent, and when stripped left a granular surface. The cortex was narrowed. The right suprarenal was soft and degenerated, the left large and firm. The heart weighed 10½ oz.; the kidneys, 7½ oz.

Histological examination. The kidneys showed an increase of interstitial connective tissue with some round-cell infiltration. The arteries were thickened. The capsule of the suprarenals was thin. Some of the outer part of the zona fasciculata was poorly stained and vacuolated. The nuclei were normal. In a few places they were absent. The pigment layer was increased in size. Fat was marked throughout the cortex, especially in the zona fasciculata. The medulla was well developed and contained a considerable amount of fat. Clumps of cortical cells, containing fat and pigment, were present in the medulla. There was a slight increase in the elastic tissue. The chrome reaction was well marked, the whole medulla staining a uniform brown colour.

Case III. Chronic interstitial nephritis and senile gangrene. E. P., female, aged 75. In hospital five months. The patient was admitted with a three weeks' history of blackening of the toes. She was found to have gangrene of all the toes of the right foot. The urine contained a trace of albumin. The heart and lungs were normal. About a month later an arterio-venous anastomosis between the femoral artery and vein was performed in Hunter's canal. Shortly after the operation the colour of the toes began to improve and a line of demarcation appeared. Four months after the operation the patient was seized with abdominal pain and died shortly afterwards. The case is reported with illustrations in the *Proceedings of the Royal Society of Medicine* for June, 1908.

Post mortem. Early peritonitis was present. The kidneys were small and the capsules were adherent to a granular surface. The right suprarenal was soft and disorganized, the left was firm and large. The vessels throughout the body were thickened. The left ventricle was hypertrophied. The heart weighed 11½ oz.; the kidneys, 6¾ oz.

Histological examination. The kidneys showed an increase of interstitial connective tissue. There was some round-cell infiltration. The glomeruli were obliterated in places. The arteries were greatly thickened. The internal elastic lamina was very much increased in size. The capsule of the suprarenals

was thin. The zona fasciculata was poorly stained and vacuolated in its outer part. Nuclei were absent in places, but for the most part were crushed to the side of the cells by large vacuoles. The inner part was well stained. The pigment layer was well marked. There was a considerable amount of fat in the cortex and a few scattered fatty acid crystals were seen. The medulla was very well developed. The elastic tissue was well marked. There was a collection of round cells near the central vessels. A small amount of fat was present. Cortical cells containing fat were seen in the medulla. The chrome reaction was well marked. In places the brown coloration was more marked than in others.

Case IV. Chronic interstitial nephritis and subacute pleurisy. H. H., male, aged 35. In hospital nineteen days. The patient had rheumatic fever sixteen months before admission. He had suffered from headache and epistaxis, and for the previous ten days his vision had become blurred. On admission the apex beat was felt in the sixth space, one inch external to the nipple line. A mitral systolic murmur was heard at the apex. The blood pressure measured 205 mm. Hg. Renal retinitis with numerous haemorrhages was present. The urine, of specific gravity 1008, contained a heavy cloud of albumin.

Post mortem. A subacute plastic pleurisy was present on the right side. The heart was greatly hypertrophied, the valves were healthy. The vessels throughout the body were thickened. The kidneys were small, red, and granular. The suprarenals showed small cortical outgrowths on the surface. The heart weighed $21\frac{1}{2}$ oz.; the kidneys, 8 oz.

Histological examination. The kidneys were both small. They showed marked interstitial changes. The vessels were very much thickened and the elastic tissue on either side of the media was increased. The capsule of the suprarenals was thin. A cortical outgrowth was seen on section, containing the three layers of the cortex, the inner part vacuolated and pigmented. Parts of the cortex proper were vacuolated. Fatty acid crystals were very plentiful. There was a slightly increased vascularity of the zona reticularis. The pigment layer was well marked. Fat was present throughout the cortex. The medulla was of fair size. It contained some fatty pigmented cortical cells. The chromaffin substance was well marked throughout the medulla. There was a small collection of round cells near a central vessel.

Case V. Chronic interstitial nephritis. T. E., male, aged 37. In hospital nine weeks. The patient had gout twenty-two years before admission and oedema of the legs and headache for one month. On admission the blood pressure measured 195 mm. Hg. The urine, of specific gravity 1016, contained albumin (one-sixth), blood, hyaline and granular casts. While in the hospital the blood pressure varied between 170 and 198 mm. Hg., being reduced to 142 mm. Hg. for a time after hot baths.

Post mortem. The lungs were oedematous; there was 10 oz. of fluid in each pleural cavity. There was plastic pericarditis. The heart was hypertrophied. There was no valvular or aortic disease. The kidneys were pale. The capsules were adherent and, when stripped, left a granular surface. The cortices were shrunken. The suprarenals were large and unduly firm. The vessels of the body were uniformly thickened.

Histological examination. The kidneys showed an interstitial nephritis with subcortical collections of round cells. The vessels were greatly thickened, with an increase in the elastic lamina. The cortex of the suprarenals was extremely fatty. Fatty acid crystals were very numerous. The zona fasciculata was poorly stained except in its inner part. There was a considerable vacuolization of the outer part. The zona reticularis was fairly vascular. The pigment layer was not well marked. The medulla was fairly well developed. It contained a small amount of fat. The elastic tissue was very well marked. There was an increased vascularity of the medulla. The chrome reaction was marked.

Case VI. Chronic interstitial nephritis and uraemia. H. P., female, aged 24. In hospital five days. For the previous twelve weeks the patient had constant haemorrhage from the gums and nostrils, and for the previous month occasional haemorrhage from the anus and vagina. On admission she was very drowsy. The area of cardiac dullness was not enlarged. A blowing systolic murmur was heard at the apex. She had several convulsions and died in one.

Post mortem. The heart was hypertrophied. There was no valvular or aortic disease. The smaller vessels were thickened. The kidneys were small and pale. The capsule was adherent. The surface was pale and granular. The suprarenals were large and firm. The heart weighed 13 oz.; the kidneys, $5\frac{1}{2}$ oz.; the suprarenals, 14.75 grammes.

Histological examination. The kidneys showed extreme interstitial change. The vessels were extremely thickened. The elastic lamina was greatly increased in thickness. The zona fasciculata of the suprarenals was poorly stained and vacuolated in its outer part. Nuclei were absent in places. It contained a large amount of fat. Fatty acid crystals were very numerous. The pigment layer was poorly developed. The elastic tissue was fairly well marked. It contained but little fat. A few cortical cells containing fat were seen in the medulla, separated from the rest of the cortex by medullary cells. The chrome reaction was marked, the brown coloration being very marked in places.

Case VII. Chronic interstitial nephritis. R. C., female, aged 56. In hospital five days. The patient was admitted with a history of constipation for a fortnight. On admission she had a high tension pulse and the urine, of specific gravity 1012, contained a small amount of albumin. Two days before her death her respiration became laboured and twitchings of the face and body were observed.

Post mortem. The heart was hypertrophied, the valves were healthy, and there was some atheroma of the aortic arch. The kidneys varied greatly in size. The left was small and markedly fibrotic with the capsule firmly adherent. The right kidney was larger and the capsule was only slightly adherent. The medium-sized arteries throughout the body did not appear to be thickened. The heart weighed $14\frac{1}{2}$ oz.; the kidneys—the right $4\frac{1}{2}$ oz., the left $1\frac{1}{2}$ oz.; the suprarenals, 10.4 grammes.

Histological examination. The kidneys showed a high degree of chronic interstitial nephritis. The vessels were very much thickened. The suprarenals had a thick capsule. The zona fasciculata was slightly vacuolated and poorly stained in places. Some cortical outgrowths were seen. Fat was present throughout the cortex, being especially marked in places. No crystals were seen. A few clumps of round cells were seen in the cortex. The pigment layer was well marked. The medulla was well developed; it contained very little fat. The chrome reaction was well marked. The brown coloration was uniformly spread throughout the medulla.

Case VIII. Chronic interstitial nephritis and symptomatic purpura. L. F., male, aged 30. In hospital six days. Seven weeks before admission, on his way home from Australia, the patient began to feel ill with headache, dizziness, bleeding from the gums, haemoptysis, and epistaxis. On admission the chest and abdomen were normal. The urine, of specific gravity 1010, contained a faint cloud of albumin.

Post mortem. The heart was hypertrophied; there was no valvular disease. The kidneys were small. The capsules were firmly adherent and left a granular surface when stripped off. The suprarenals were large and firm.

Histological examination. The kidneys showed a very marked increase of interstitial connective tissue with round-cell infiltrations. The vessels were very much thickened. The elastic tissue was well marked. The cortex of the

suprarenals was well stained and slightly vacuolated and contained a considerable amount of fat in the middle of the zona fasciculata. A few crystals were seen. The pigment layer was fairly well developed. Fatty cortical cells were present here and there. The elastic tissue was well developed; the medullary sinuses were large. A small amount of fat was present. The chrome reaction was well marked throughout the medulla.

Case IX. Chronic interstitial nephritis, chronic pleurisy, &c. T. F., male, post office pensioner, aged 51. In hospital five weeks. The patient had had oedema of the legs and polyuria for the last three years. On admission the vessels were thickened; the blood pressure measured 170 mm. Hg. The urine contained albumin (2.5 grammes per litre).

Post mortem. Both pleural sacs were obliterated by dense adhesions. The pericardium was adherent to both lungs and to the anterior thoracic wall. The left ventricle was greatly hypertrophied. There was some atheroma of the aorta. The kidneys were small and pale. The capsules were adherent, the surfaces were granular. Weight of the organs: heart, 19½ oz.; kidneys, 6½ oz.; suprarenals, 9.65 grammes.

Histological examination. The kidneys showed a great increase of interstitial connective tissue. The vessels were greatly thickened and the elastic tissue was markedly increased. The capsule of the suprarenals was thin. The cortex was very vacuolated in places. Fat was present throughout the cortex, very marked in places. No crystals were seen. The pigment layer was fairly well developed. The medulla was well developed. It contained several fatty cortical cells. The elastic tissue was fairly well developed. Chromaffin substance was very well marked. In places the brown coloration was much deeper than in others.

Case X. Chronic interstitial nephritis and cardiac dilatation. E. T., female, barmaid, aged 36. In hospital thirteen days. The patient had suffered from oedema of the legs for the preceding four years. On admission there was oedema of the legs, ascites, and signs of pleural effusion. The pulse was of high tension. The urine contained a cloud of albumin and hyaline and granular casts.

Post mortem. There was fluid in all the serous cavities. There was hypertrophy of the left ventricle. There was no valvular disease. The kidneys were large and their capsules stripped off fairly easily. The pyramids were congested.

Histological examination. The kidneys showed an interstitial nephritis. There was a slight thickening of the vessels. There was some increased vascularity present. The capsule of the suprarenals was thin. The cortex was poorly stained and highly vacuolated. The fat was well marked. Large clumps of fatty acid crystals were seen. The zona reticularis was very vascular. The pigment layer was well marked. The medulla was well developed. It contained some fat and pigmented cortical cells. The elastic tissue was increased in amount. The chrome reaction was marked.

Case XI. Chronic interstitial nephritis and tubercular laryngitis. H. G. W., male, mechanical engineer, aged 43. In hospital five days. Eight weeks before admission his voice became husky and he was told he had some kidney trouble. On admission his urine, of specific gravity 1015, contained blood and a small amount of albumin.

Post mortem. He was found to have tubercular laryngitis and tubercular deposits throughout both lungs. The left ventricle of the heart was hypertrophied, the valves were healthy. The kidneys were very small. The capsules were adherent and left a granular surface when stripped off. The suprarenals were large and firm. There were no macroscopical signs of tuberculosis in either kidneys or suprarenals. The heart weighed 16½ oz.; the kidneys, 7½ oz.; and the suprarenals, 13.6 grammes.

Histological examination. There were no signs of tuberculosis in either kidneys or suprarenals. The kidneys showed extreme interstitial nephritis. There was considerable vascularity. Stained with methyl violet, amyloid change was seen throughout the kidney. The amyloid change in the suprarenals was well seen in the vessels running in the cortex between the columns of the zona fasciculata. These latter cells appeared to be crushed by the amyloid deposit. Fat was scattered in patches throughout the cortex. No crystals were seen. The pigment layer was poorly developed. The medulla was fairly well developed. It contained a considerable amount of fat. A large part was occupied by the amyloid substance. The chromaffin reaction was present to a moderate degree.

Case XII. Chronic interstitial nephritis and cerebral haemorrhage. W. T. B., male, aged 39. In hospital one day. No history of the patient's history was obtainable. He was unconscious on admission and died soon afterwards.

Post mortem. The legs were slightly oedematous. A large haemorrhage had ploughed up the neighbourhood of the left lenticular nucleus and had burst into the ventricles. The heart was greatly hypertrophied, the valves were healthy. All the vessels of the body were thickened. The kidneys were typically red and granular. The suprarenals were firm and large. The heart weighed 22½ oz.; the kidneys, 9½ oz.; the suprarenals, 15.48 grammes.

Histological examination. The kidneys showed a condition of interstitial nephritis. The vessels were thickened and congested. The elastic lamina was greatly increased in size. Round-cell infiltrations were present. The zona glomerulosa of the suprarenals was well stained and slightly vacuolated. The rest of the cortex was poorly stained and very much vacuolated. In places the nuclei were absent. The zona reticularis was wide and very vascular. The pigment layer was very marked and extended throughout the zona reticularis. Fat was very marked throughout the cortex. The medulla was very well developed and very vascular. It contained a small amount of fat. Several fatty cortical cells were seen scattered about the medulla. There were small collections of round cells in the medulla surrounding the central vessels. The chrome reaction was marked.

Case XIII. Chronic interstitial nephritis and cardiac failure. R. C., male, aged 16, errand boy. In hospital fourteen days. One month before admission the patient had an attack of haematuria, and for the preceding fourteen days his legs and face had been swollen. On admission there was considerable oedema of the legs and face. The pulse tension registered 145 mm. Hg. The urine, of specific gravity 1010, contained a large amount of albumin. A few granular casts were seen. Shortly before his death breathing became difficult and vomiting set in. No twitches or convulsions were seen.

Post mortem. There was oedema of face, scrotum, legs, pharynx, glottis, and lungs. The left ventricle was hypertrophied and dilated. There was no valvular disease. There was slight atheroma of the aortic arch. The kidneys were slightly enlarged. Their capsules were thick and adherent, and left a granular surface when stripped off. The heart weighed 15 oz.; the kidneys, 12½ oz.; the suprarenals, 6 grammes.

Histological examination. The kidneys showed a great increase of interstitial connective tissue with round-cell infiltrations. There was considerable thickening of the vessel walls. The outer part of the zona fasciculata of the suprarenals was well stained, the inner part vacuolated. The zona reticularis was very vascular. The pigment layer was fairly well developed. The fat was very marked in the middle part of the zona fasciculata. The medulla was fairly well developed and the chromaffin reaction was very well marked. A small amount of fat was present. The elastic tissue was increased in amount. There were collections of round cells surrounding the central vessel of the medulla.

Case XIV. Abdominal aneurysm and chronic interstitial nephritis. C. B., male, coal dealer, aged 30. In hospital eleven weeks. The patient contracted syphilis in 1894 and was treated for two months. He had noticed a pulsating epigastric tumour for the last seven years. On admission the apex beat was situated in the fifth space just external to the nipple line. The arteries were thickened and the pulse tension measured 155 mm. Hg. The epigastric swelling reached to one inch above the umbilicus. The urine, of specific gravity 1022, contained a cloud of albumin. The abdominal swelling gradually diminished in size during the patient's stay in hospital. On the day of his death patient developed an aneurysmal cough. His speech became blurred, and he experienced some difficulty in swallowing. He developed ptosis of the left eye.

Post mortem. There was a fusiform aneurysm of the abdominal aorta filled with laminated clot. The heart was hypertrophied, the valves were healthy. All the vessels of the body were thickened and rigid. The left vertebral artery contained a small white embolus plugging the artery at the origin of the posterior inferior cerebellar artery. The kidneys were enlarged. The capsules were adherent and, when stripped off, left a granulated surface. The heart weighed 22½ oz.; the kidneys, 15¾ oz.

Histological examination. The kidneys showed a marked degree of interstitial nephritis with round-cell infiltration and thickened vessels. The elastic tissue was greatly increased in amount. There was marked vascularity. The connective-tissue capsule of the suprarenals was thickened. Several cortical adenomata were present. The zona reticularis was poorly stained and vacuolated. The pigment layer was marked. There was a considerable amount of fat throughout the cortex. The medulla was well developed and contained large sinuses. Several clumps of cortical cells were present. Elastic tissue was marked. There was no increased vascularity. The chrome reaction was well marked.

Case XV. Stokes-Adams disease and chronic interstitial nephritis. M. S., male, army pensioner, aged 70. In hospital a few hours. For the past two years he had been subject to fits. He was sent up to the hospital unconscious after having had fifty-two fits. He died shortly afterwards.

Post mortem. The heart was only slightly enlarged. The aortic valves were calcified. This calcification appeared to have involved the upper portion of the bundle of His. The kidneys were small. The capsules were firmly adherent and left a granular surface when stripped off. The suprarenals were large. There was no lesion in the brain or cerebellum. The heart weighed 13 oz.; the kidneys, 10 oz.; the suprarenals, 12.65 grammes.

Histological examination. The kidneys showed a marked increase of interstitial connective tissue and subcapsular collections of round cells. The vessels were moderately thickened and engorged with blood. The left suprarenal was soft and friable, the right firm and large. The connective-tissue capsule was rather thicker than normal. There were several cortical outgrowths seen, partly embedded in the zona fasciculata and partly raised above the surface of the gland. The zona fasciculata was well stained and contained a considerable amount of fat. There was marked congestion of the zona reticularis. The pigment layer was well marked. A few fatty acid crystals were seen. The medulla was of large size. It contained a slight amount of fat and elastic tissue. It was very vascular, and clumps of round cells were seen near the central vessel. The chrome reaction was well marked.

Case XVI. Ulcerative endocarditis and chronic interstitial nephritis. W. S., male, bottle-blower, aged 30. In hospital four weeks. On admission the apex beat was half an inch external to the nipple line in the fifth space. A mitral systolic murmur was heard, also a soft aortic diastolic. The pulse was collapsing

and of a high tension. The urine, of specific gravity 1009, contained blood and albumin (about $1\frac{1}{2}$ grammes per litre). The temperature was normal till the day before his death, when he had a rigor.

Post mortem. The heart was greatly enlarged. The aortic valves were incompetent. There was recent endocarditis present, with large vegetations on the site of an old sclerosing endocarditis. One valve was perforated. The mitral valve had large globular vegetations. The kidneys were grossly diseased. The cortex showed loss of all detail and a general mottling. The capsules stripped fairly well. The heart weighed $17\frac{3}{4}$ oz.; the kidneys, $21\frac{1}{2}$ oz.

Histological examination. The kidneys showed interstitial with some slight parenchymatous change. There was intense vascularity throughout the section. The cortex of the suprarenals was poorly stained and vacuolated in places. Only a small amount of fat was present. Several crystals were seen. Several adenomata were present, one containing a considerable amount of fat. There was intense vascularity of the zona reticularis. The pigment layer was well marked. The medulla was very well developed. The chrome reaction was very marked. It was very vascular and contained several clumps of pigmented cortical cells. A considerable amount of fat was present in the medulla.

Case XVII. Acute and chronic interstitial nephritis. A. S., male, lawyer's clerk, aged 49. In hospital three weeks. Five weeks before admission he suffered from cough and pain between the shoulders. A doctor told him he had some kidney trouble. His legs were swollen for the previous month.

On admission there were signs of a pleural effusion on the right side. The cardiac impulse was seen in the fifth space in the nipple line. His pulse tension was 170 mm. Hg. The urine contained much albumin and blood. Granular and epithelial casts were seen.

Post mortem. The penis and scrotum were oedematous. There was an excess of fluid in the pleural and pericardial cavities. The heart was hypertrophied. There was no valvular disease. The kidneys were large and congested. The capsules stripped well. The heart weighed 15 oz.; the kidneys, $17\frac{3}{4}$ oz.; the suprarenals, 12.9 grammes.

Histological examination. The kidneys showed acute nephritis superimposed on a chronic interstitial nephritis. There was considerable fatty change in the tubules. The vessels were not thickened. The capsule of the suprarenals was thick. The zona fasciculata was very much vacuolated and poorly stained. The zona reticularis was very vascular. The pigment layer was increased in size. There was marked fatty change throughout the cortex. The medulla was large and very vascular. A small amount of fat was present. The elastic tissue was increased in amount. Several clumps of round cells were seen. The chrome reaction was well marked, the brown colour being very intense throughout the medulla.

The following three cases show hypertrophy of the left ventricle without any interstitial change in the kidneys:—

Case XVIII. Aortic aneurysm and hypertrophy of the left ventricle. C. B., male, aged 32. In hospital one month. The patient gave a history of syphilis and alcohol. For the last three months he had suffered from dyspnoea and oedema of the legs. Ascites developed one month before admission. On admission there were signs of an aneurysm of the thoracic aorta. A double aortic murmur was heard. The urine, of specific gravity 1010, contained a large amount of albumin. Ascites was present.

Post mortem. The heart was greatly enlarged. The aorta was uniformly atheromatous. Just above the aortic cusps on the right of the aorta was the opening of an aneurysmal sac. This led into a cavity the size of an orange, which formed a bulging prominence in the right ventricle. The cardiac valves

were healthy. The kidneys were deeply congested. The capsules stripped well. The kidneys weighed $14\frac{1}{2}$ oz.; the suprarenals, 9.15 grammes.

Histological examination. The kidneys showed no signs of interstitial change. There was no increase in the size of the vessels or of the elastic tissue. The capsule of the suprarenals was slightly increased in size; prolongations of it ran down between the columns of the zona fasciculata. The vessels were engorged with blood, as was the zona reticularis. The pigment layer was well marked. The cortical cells were slightly vacuolated. Fat was well marked throughout the cortex. The medulla was well developed. It contained a considerable amount of elastic tissue. Several clumps of fatty cortical cells were present. Chromaffin substance was present in large quantities, the brown colour of the medulla being very marked.

Case XIX. Aortic disease and hypertrophy of the left ventricle. A. C. P., male, engineer, aged 51. In hospital eleven weeks. There was no history of rheumatic fever. The patient had contracted syphilis thirty-three years previously. He began to get short of breath one year ago, and for the last four months following an attack of influenza he had suffered from oedema of the legs.

On admission the apex beat was seen in the fifth space one inch external to the nipple line. A presystolic and systolic murmur was heard at the apex and a double murmur was heard at the aortic cartilage. The liver reached to the umbilicus. The urine, of specific gravity 1022, contained a cloud of albumin.

Post mortem. The pericardial and pleural cavities contained an excess of fluid. The thoracic aorta was greatly diseased from one inch above the aortic valves. The aortic valves were atheromatous and incompetent. The mitral valves were slightly thickened. The left ventricle was greatly hypertrophied. The kidneys were large and congested. The left suprarenal was large and had a large medulla; the right was small and had a small medulla. The heart weighed 19 oz.; the kidneys, $10\frac{1}{2}$ oz.; the suprarenals, 9.5 grammes.

Histological examination. The kidneys showed great vascularity. No interstitial change was present. The vessels were not thickened. The cortical cells of the suprarenals were vacuolated. The zona reticularis was very vascular and the pigment layer was very marked. Fat was present throughout the cortex. The medulla was fairly well developed. It contained a small amount of fat. Several clumps of fatty cortical cells, containing pigment, were present in the medulla. The chromaffin reaction was present in moderate quantities.

Case XX. Cerebral haemorrhage and hypertrophy of the left ventricle. D. L. L., male, aged 46. In hospital a few hours. The patient was unconscious on admission, and no history of his illness was obtained.

Post mortem. There was a haemorrhage into the pons Varolii, and old haemorrhages into the lower half of the pons and right cerebral hemisphere were seen. The internal capsules were not involved. The vessels at the base of the brain were thickened and atheromatous. The heart was hypertrophied. The kidneys were large and congested. All the arteries of the body were thickened. The suprarenals were firm and very large. The heart weighed $23\frac{1}{2}$ oz.; the kidneys, $12\frac{1}{4}$ oz.; the suprarenals, 22.6 grammes.

Histological examination. The kidneys were very vascular. No interstitial change was present. The vessels were not thickened. The cortex of the suprarenals was poorly stained and very vacuolated. It contained a considerable amount of fat. The zona reticularis was very vascular and the pigment layer was very marked. Clumps of fatty acid crystals were seen. The medulla was large and contained a few cortical cells. The chrome reaction was fairly well marked.

Five cases of wasting disease with presumably low blood pressure.

Case XXI. Diabetes. A. H., female, cook, aged 37. In hospital seven weeks. The patient was said to have had diabetes in 1903. She was admitted to the hospital in 1902 and 1905, and then was passing sugar in her urine (between 16 and 30 grains per oz.). On admission she was found to have gangrenous patches on both feet. The urine measured about 70 oz. per diem, of specific gravity 1040, and contained 18 grains of sugar per ounce. She weighed 3 st. 13½ lb.

Post mortem. The body was extremely emaciated. The heart was small. The arteries were healthy. The kidneys were rather large. The heart weighed 4½ oz.; the kidneys, 9¼ oz.

Histological examination. The kidneys showed no signs of nephritis. They were slightly vascular. There was no thickness of the vessels. The capsule of the suprarenals was thick. The cortex was poorly developed and vacuolated. There was some increase of connective tissue between the columns of the zona fasciculata. The zona reticularis was vascular and the pigment layer was well marked. Fat was present throughout the cortex and a few small crystals were seen. The medulla was small and contained several clumps of pigmented cortical cells. It was very vascular and slightly fatty. A small amount of chromaffin substance was present, the brown coloration being very faint. There was a large amount of connective tissue throughout the medulla.

Case XXII. Pernicious anaemia and pneumonia. E. D., female, aged 42. In hospital ten days. The patient was known to have pernicious anaemia six months before admission. On admission the blood examination showed typical signs of this disease. The urine contained a cloud of albumin. She weighed 8 st. 7½ lb. Three days before death she became drowsy and Cheyne-Stokes breathing developed.

Post mortem. The upper half of the left lung showed red hepatization with a thin layer of fibrin on the pleura. The liver gave a slight free-iron reaction. The kidneys were pale; the cortices were slightly atrophied and showed a good free-iron reaction. A blood culture gave a pure culture of streptococcus pyogenes. The heart weighed 12 oz.; the kidneys, 9¼ oz.

Histological examination. The kidneys showed the presence of free iron in the tubules. There was some slight patchy increase of connective tissue. The vessels were not thickened. The suprarenals did not give a free-iron reaction. The cortical cells were fairly well stained. Fat was present in small quantities throughout the cortex. No crystals were seen. No pigment was seen in the zona reticularis. The medulla was very narrow. Only a small amount of chromaffin substance was seen. The brown coloration was very faint.

Case XXIII. Diphtheria. J. J., male, aged 4. In hospital three days. There was a two days' history of sore throat, followed by dyspnoea the next day. On admission he was cyanosed and restless. Stridor was present on respiration. Both tonsils were covered with a thick white membrane. Tracheotomy was performed soon after admission, and 12,000 units of antitoxin administered. The colour improved and the stridor disappeared, but relief was not absolute. During the night a bronchial cast, five inches long, was coughed up; this gave him considerable relief. The next night he again became restless and cyanosed and died shortly afterwards from asphyxia.

Post mortem. The laryngeal aperture was partly occluded by membrane. A layer of thick and tenacious membrane lined the trachea. No bronchopneumonia was present. The right cavity of the heart was distended with a whitish clot. The heart weighed 4 oz.; the kidneys, 4½ oz.

Histological examination. The cortex of the suprarenals was well preserved. Several adenomata were present. There was no vacuolization. There was no pigment present in the zona reticularis. The medulla was fairly well

developed. The sinuses were engorged with blood, and there was one large haemorrhage in the centre. Only a small amount of chromaffin substance was seen.

Case XXIV. Carcinoma of the pylorus. S. S., male, shoemaker, aged 54. In hospital two weeks. The patient had suffered from indigestion for the previous five months. On admission he was thin and anaemic. A hard smooth lump was felt in the epigastrium on the left side. It was fairly movable in all directions, except downwards. The urine, of specific gravity 1007, did not contain any albumin. At the operation a mass, the size of a cricket ball, was found at the pylorus. A posterior gastro-jejunostomy was performed, but the patient died five days later.

Post mortem. A large tumour occupied the pyloric end of the stomach, extending four inches backwards from the pyloric ring. The adjacent lymph glands were enlarged. The heart weighed 9 oz.; the kidneys, 8½ oz.; the suprarenals, 7.4 grammes.

Histological examination. The growth in the stomach consisted of a columnar-cell carcinoma. The kidneys showed no interstitial changes. The vessels were not thickened. The suprarenals showed no signs of carcinoma. The capsule was very thick. The cortex was vacuolated and poorly stained. Fat was well marked throughout the cortex. No crystals were seen. The pigment layer was fairly well marked. The medulla was very small. A few cortical cells were present in its centre. There was an increase of connective tissue present. A small amount of chromaffin substance was present here and there in the medulla.

Case XXV. Carcinoma of the stomach. P. L. T., male, aged 60. In hospital seventeen days. The patient first noticed some discomfort in the abdomen three months before admission. For the last month the pain had been severe. On admission his weight was 7 st. 13 lb. No mass or peristalsis was seen. The right rectus was rigid and tender. There were signs of a left pleural effusion. One pint of fluid was withdrawn by aspiration.

Post mortem. Nodules of growth were seen sprouting through the diaphragm on the left side. The stomach was full of a fungating necrotic growth. The oesophageal and pyloric ends had escaped the growth. It extended into the spleen, head of the pancreas, and the left lobe of the liver. The portal vein was distended with growth. The kidneys were pale and wasted. Their capsules stripped off well. The heart weighed 10 oz.; the kidneys, 9 oz.; the suprarenals, 7.75 grammes.

Histological examination. The kidneys did not show any interstitial change. The arteries were slightly thickened. The capsule of the suprarenals was thick. The cortex was well preserved and stained. A few vacuolated patches without any nuclei were seen. A small cortical outgrowth was seen. The connective tissue between the columns of cortical cells was increased in amount. Fat was present in small quantities throughout the cortex. The pigment layer was fairly well developed. Clumps of round cells were seen in the cortex. The medulla was very narrow. The connective tissue was increased in amount. Several clumps of cortical cells were seen in its centre. Only a small amount of chromaffin substance was present.

In order to show that, after treatment with Orth's fluid and Scharlach R., the brown coloration of the medulla resulting was due to the Orth's fluid and not to the Scharlach, different methods of staining were adopted in two cases.

Sections were fixed in salt formalin and stained with Scharlach or mounted unstained. Others were fixed in Orth's fluid and treated in the same way. The results of these investigations showed that the medulla of the salt formalin sections, whether they were stained with Scharlach or not, remained unstained, whilst the medulla of the sections fixed in Orth's fluid appeared a deep brown colour.

Case XXVI. Pericarditis and chronic interstitial nephritis. J. G., male, aged 27. In hospital nine days. There was no history of rheumatic fever. On admission the area of cardiac dullness was enlarged. A pericardial friction rub was heard over the base of the heart. No endocardial murmurs were heard. There was slight oedema of the feet. The urine contained a cloud of albumin.

Post mortem. The heart was greatly enlarged and its surface was covered with fibrin. The left ventricle was enormously hypertrophied. There was no valvular disease. The kidneys were congested. There was a slight narrowing of the cortices. The capsules stripped well and left a slightly granular surface. The suprarenals were large and well preserved. Small adenomata were present on the surface. The medulla was large. An accessory suprarenal was seen lying in the surrounding fatty covering. The heart weighed 21½ oz.; the kidneys, 9¼ oz.; the suprarenals, 12.7 grammes.

Histological examination. The kidneys showed great increase of interstitial connective tissue. The vessels were not greatly thickened. There was a considerable vascularity. The sections of the suprarenals fixed in Orth's fluid and mounted unstained showed a brown medulla and a clear unstained cortex; those fixed in salt formalin and mounted unstained were colourless. The salt formalin sections stained with Scharlach showed a markedly fatty cortex with an unstained medulla dotted over with minute fat droplets. The cells of the cortex were well stained. Several large and small adenomata were present. The fat was well marked. A few scattered crystals were seen. The medulla was very large. It contained a fair amount of fat. A few nerve ganglia were cut on section. Several clumps of fatty cortical cells were seen in the medulla. The chrome reaction was very marked.

Case XXVII. Chronic interstitial nephritis and adenoma of the prostate. W. T. A., male, aged 79, in hospital forty days. The patient was operated on for adenoma of the prostate three days after admission. The adenoma weighed 140 grammes.

Post mortem. The kidneys were small and studded on the surface with small yellow spots. The capsule was slightly adherent and left a rough granular surface. Pus was seen in the pelvis, and pyramids also scattered over the surface of the kidney. The arteries were atheromatous and calcareous. The heart and other organs were healthy. The kidneys weighed 9¼ oz.

Histological examination. The kidneys showed chronic interstitial nephritis and a condition of 'surgical kidney'. The sections fixed in Orth's fluid and mounted unstained showed a brown medulla of the suprarenals; those fixed with salt formalin and mounted unstained, a colourless one. The capsules were very thick. Several small adenomata were present. The cortical cells were well preserved. Fat was present in large quantities in the inner part of the zona fasciculata. No crystals were seen. The zona reticularis was very vascular. The medulla was well developed. It was very vascular. It contained several clumps of cortical cells. The chrome reaction was very marked.

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ON THE DIURESIS OF CHILL

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It is a matter of common knowledge to observant persons that on exposure of the body to cold an extra quantity of urine, very pale in colour, is excreted during and after the exposure. On imagining the physiological conditions which might lead up to such extra secretion it might at once be attributed to the transference to the urinary secretion of that amount of water which would have been given off by the skin, but which, owing to peripheral vaso-constriction, has not been given off in such a manner. On several occasions, however, the writer has had it forced upon his attention that on working in a cold room (reading, &c.) the amount of urine produced has been so large as to suggest other sources of the production of water. The experiments to be detailed hereafter were undertaken in order to attempt to solve the problem, and, in particular, first, whether an actual increase in water excretion does take place, and secondly, to ascertain the source of that increase, if present.

The effect of cold on the animal body.

Notwithstanding the large amount of attention devoted to the effect of heat and cold on the body as a therapeutic measure, the particular problem here put forward does not appear to have been the subject of any exact researches in modern literature. The only references to diuresis after an extended search of scientific writings are in v. Ziemsen's *Handbuch* (1886), in an article by Winternitz, and in Halliburton's *Textbook of Physiology*. Winternitz says (p. 446), 'External applications (thermal) will act on the functions of the kidneys only in so far as they control innervation and the circulation or alter the blood pressure and distribution of blood. The experimental basis on which is placed the statement that by cold applications to the skin we can quantitatively alter the excretion of urine, has been handed down to us by Colomann and Müller; still, so far as I know, the influence of external thermal conditions upon the secretion of urine has not been sufficiently investigated, especially as regards the qualitative alterations that the urine undergoes in thermal operations; concerning this question we nowhere find precise answers. The heightening of the pressure in the vascular system induced by cold seems to cause the diuretic action of the low temperature; on the other hand, the usually rapidly disappearing albuminuria, which is often observed after very cold baths, may find its explanation in the lowering of the blood pressure, which must take place during the period of the reaction.' Halliburton states that the secretion of urine is increased by vaso-constriction of vascular areas other than the kidney, and instances the increased production of urine in cold weather.

Other effects of cold on the body have been more carefully studied; of these

may be mentioned increased specific gravity of the blood (Lloyd Jones), polycythaemia (Thayer, Winternitz, Knopfmacher, Grawitz), increase of blood pressure, lessened elimination from the skin and hyperaemia of the internal organs. In animals, and sometimes even in man, more pronounced effects are noticed, and of these may be mentioned haemoglobinuria and haemoglobinaemia, glycosuria, inflammations of internal organs, thrombosis of vessels, petechial haemorrhages of the pleura, &c., &c.

The animal experiments done on the effect of cold have for the most part been rather violent measures, such as the immersion of an animal in ice-cold water for periods of one minute and upwards, experiments which in addition to the effect of cold include a certain amount of shock. In the experiments undertaken in this research violent measures or extreme cold has been carefully avoided, and the effects of the exposure are, therefore, the more certainly due to cold alone.

Methods.

It was thought at first that the problem could be easily solved by using small animals, such as the guinea-pig, in a respiration apparatus, the chamber being subjected first to ordinary temperatures and then to colder, but the results given in a somewhat long list of experiments have been most inconstant. It is difficult to be sure of washing all the condensed moisture out of the respiration chamber, and on subjecting the chamber to cold this moisture is considerable; again, even though precautions were taken to express the urine from the bladder of the animal before and after the experiment, it could never be done with the certainty that all had been expelled.

This method, therefore, was entirely given up, and experiments were made on man. They were always begun rather early in the morning, so as to avoid any error due to the taking of food, and the usual procedure was to empty the bladder on first waking and save the samples passed at the end of every subsequent half-hour until the experiment ended. During the first half-hour period the subject remained warm in the recumbent position; then the clothes were removed for periods varying from half an hour to $2\frac{1}{2}$ hours. At the end of each half-hour period the haemoglobin content of the blood was determined, and in some experiments the maximum and minimum blood pressure, using the Riva Rocci instrument. Owing to the conditions of the experiments it was not possible to standardize the degree of cold, which in its effect on the subject varied with the temperature, the amount of moisture, and the presence or absence of air currents.

A word or two should be said on the determination of the haemoglobin. By using Haldane's modification of Gowers' method, which after some practice is accurate to about 2 per cent. or perhaps less, it was thought that a good indication would be obtained of the concentration of the blood and thereby a clue to the source of any increase of the water excretion. But for this purpose the method is wholly unreliable; an increase in the haemoglobin percentage as measured by the haemoglobinometer does certainly take place,

but from such it cannot be inferred that the whole blood of the body is concentrated. The local disturbances of circulation are so potent in altering the concentration of the blood in the capillaries, the mere immersion of one hand in cold water being sufficient to alter the haemoglobin percentage, that the method cannot be used for this purpose. The conclusion arrived at after experimentation in this way is confirmed amply by the researches of such writers as Lloyd Jones, G. Oliver, Desbonis, and Langlois working with other methods. and is entirely confirmed in a research by T. B. Heaton, undertaken with the haemoglobinometer at my suggestion. The power of local stasis of the blood-stream in causing a concentration of the blood may be illustrated by the results of blood counts reported by G. A. Gibson from a case of chronic mediastino-pericarditis in which the arterial blood count gave 7,000,000 red cells to the cubic millimetre, the capillary blood 8,500,000, and the venous blood 10,000,000. The local blood stasis shown by the blueness of the nose and finger-tips in cold surroundings may, therefore, entirely obscure any effect on the blood itself as it occurs in the cardiac chambers; and in the details of the following experiments, when haemoglobinometer readings have been made, they must be taken merely as a confirmation of the well observed fact that after exposure to cold a certain amount of local concentration of the blood takes place. Another error in these observations, unless special precautions are observed, is that in ordinary capillary haemorrhage, such as is used for obtaining the blood for estimation of the haemoglobin, a varying amount of lymph is always present from the extra-vascular tissues which are tapped at the same time. This has been well demonstrated by G. Oliver.

Details of some experiments.

Experiment 2. March 1, 1906. Subject A. G. G.; temperature of room 42° F. The experiment began at 6.40 a.m., and the subject was exposed naked in the recumbent position near the open window from 7.10 to 8.10. There was some shivering but no great sensation of cold. The actual figures are graphically represented in the accompanying diagram, where it will be seen that the haemoglobin percentage rose during the exposure and fell gradually after, the amount of urine passed during each half-hour rose to more than double that passed during the first half-hour, and at the end of the exposure the amount passed was over 140 c.c. The amount of urine passed was great, probably being due to its being a very raw morning with a bleak wind. The specific gravity falls with the rise in the amount passed, while the total amount of solids passed increases towards the end of the exposure. The reaction of the urine becomes less acid. The total amount of urine passed during the period of the experiment was 290 c.c., and if 10 c.c. per half-hour, being the amount passed in the preliminary half-hour not under exposure, be taken as the normal amount, the total extra amount of urine passed as the result of cold is $290 - 90 = 200$ c.c.

Experiment 3. March 6, 1906. Subject A. G. G.; temperature of room 54° F. The experiment began at 6.5 a.m.; exposure to cold by removal of clothes from

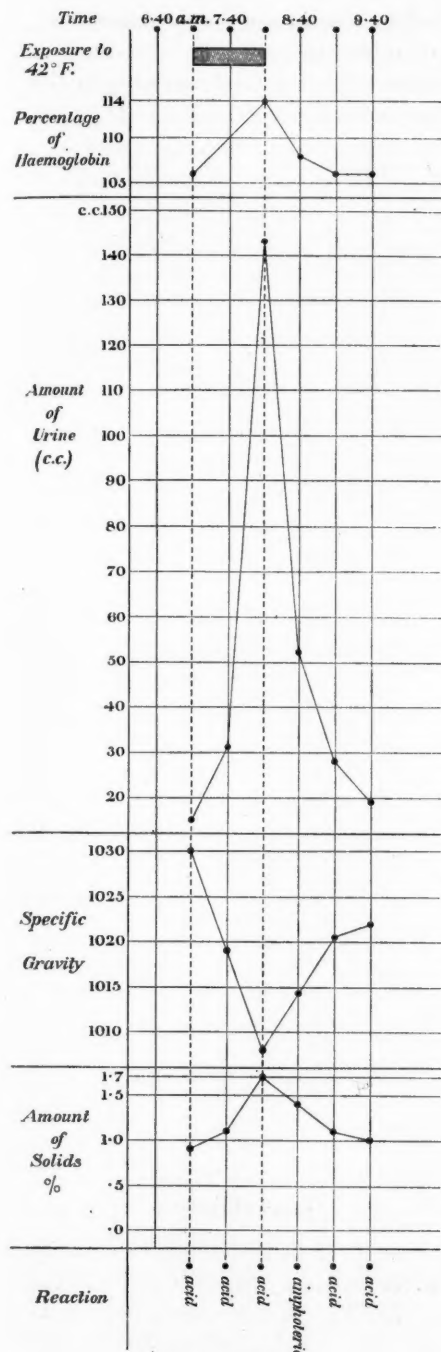


FIG. 1 (Exp. 2).

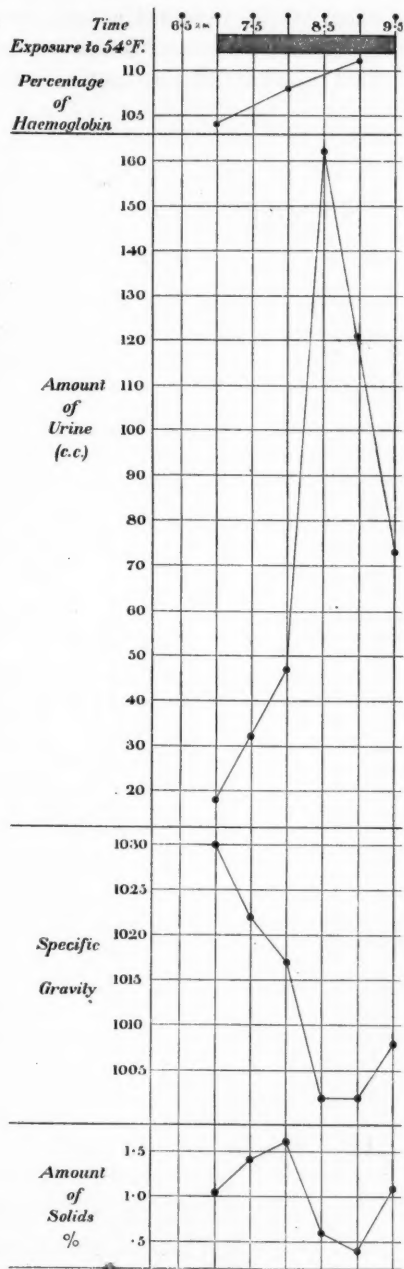


FIG. 2 (Exp. 3).

6.35 to 8.35. The same features are noticed here as in the former experiment, though being longer the total amount of urine produced is greater, namely, 452.5 c.c.; calculating in the same manner as before the total normal urine for that period as 105 c.c., the total extra urine produced is $452.5 - 105 = 347.5$ c.c.

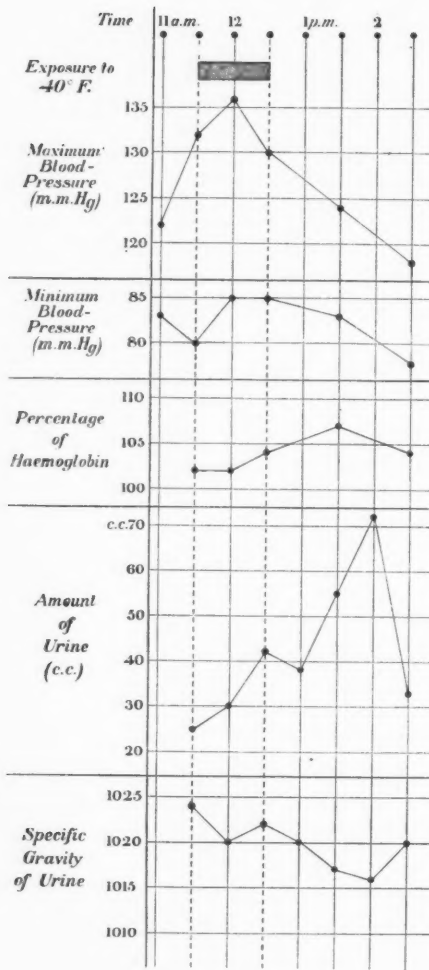


FIG. 3 (Exp. 5).

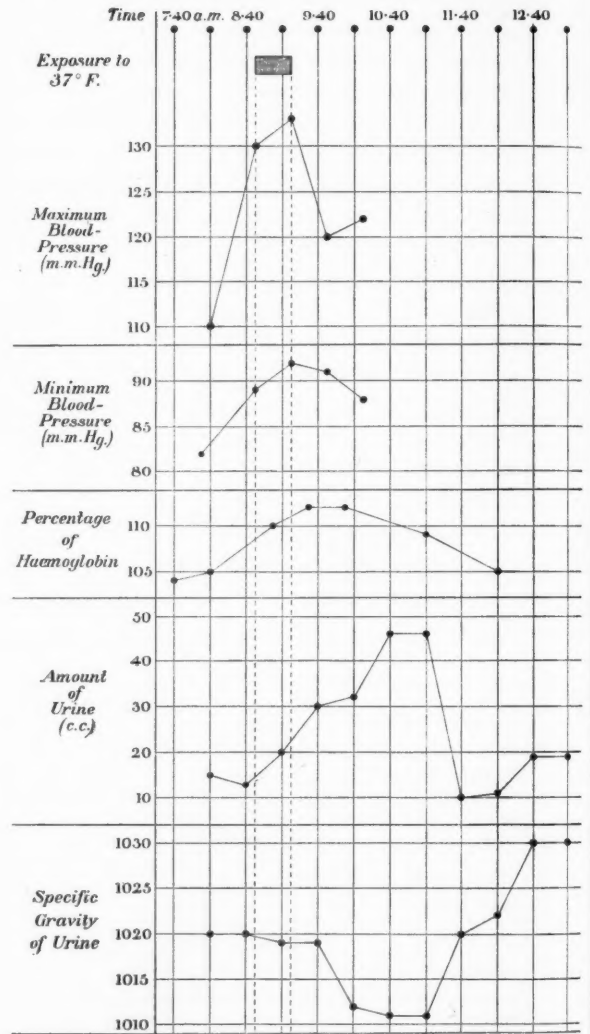


FIG. 4 (Exp. 6).

Experiment 5. May 13, 1906. Subject A. G. G.; exposure to cold by remaining naked in a cold chamber at 40°F. for one hour. In this experiment the blood pressures were measured by the Riva Rocci apparatus and readings made of the maximum and minimum pressures, using Strasburger's method for the minimum pressure. The maximum pressure rises quickly on exposure and falls

more slowly after, the minimum pressure rises somewhat slower and falls slowly afterwards. The remarkable feature about the quantities of urine passed is that the maximum quantity passed in one period occurs two hours after the exposure has terminated. The total extra urine calculated as before is $292 - 175 = 117$ c.c.

Experiment 6. May 20, 1906. Subject A. G. G.; exposure for half an hour

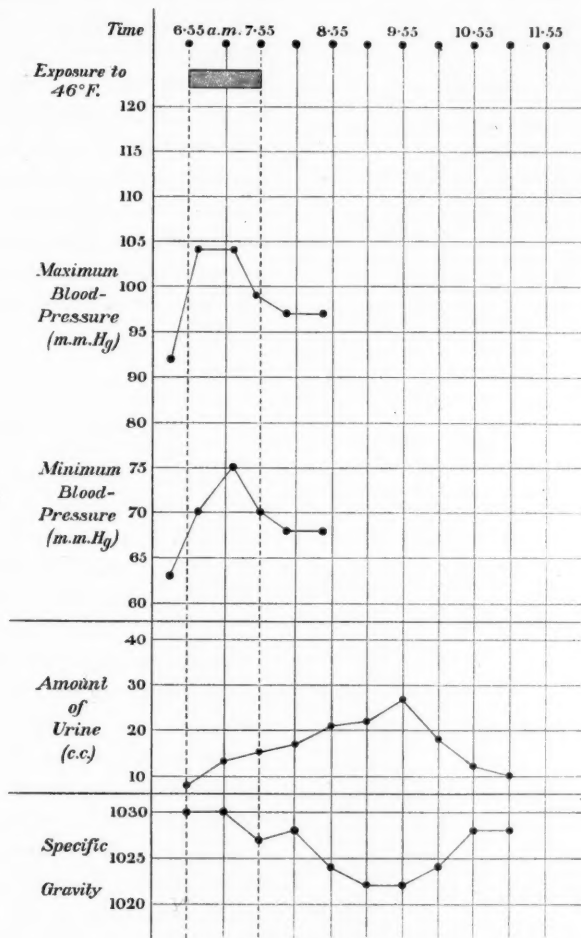


FIG. 5 (Exp. 8).

in the cold chamber at 37° F. The same features are again observed, the maximum quantity of urine being $1\frac{1}{2}$ hours after the cessation of the exposure. The total urine passed in this experiment was 263.5 c.c., and the total extra would be $263.5 - 150 = 113.5$ c.c.

Experiment 8. March 23, 1907. Subject G. E. D.; temperature of room 46° F. Exposure to cold for one hour. Total amount of urine produced =

178.6 c.c. Total extra amount = $178.6 - 90 = 88.6$ c.c. There was only slight shivering during the experiment.

Experiment 9. March 21, 1907. Subject G. E. D. Instead of being exposed to cold the subject was kept recumbent at the normal temperature, and for one hour the legs were moderately tightly bound up as far as the knees in Esmarch's bandages. Total urine produced in three hours = 80 c.c. Total extra amount is $80 - 60 = 20$ c.c.

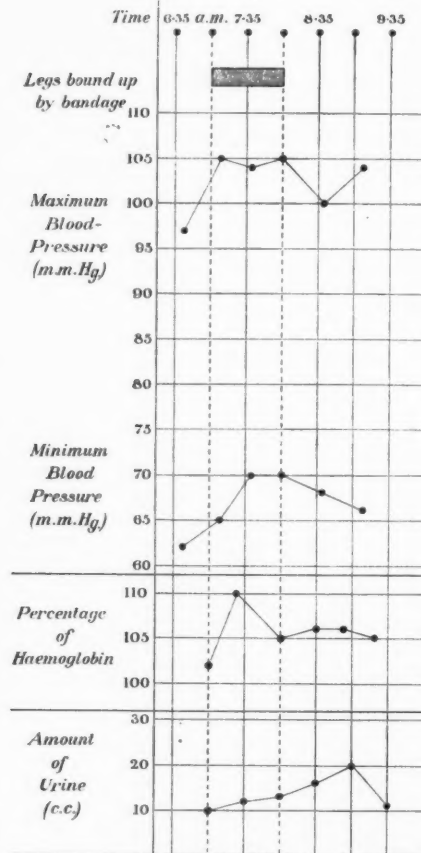


FIG. 6 (Exp. 9).

estimate for the amount of skin loss per hour as 27.8 c.c.,¹ the total amount of water given off by this means would come to 97.3 c.c. and 83.4 c.c. in Experiments 2 and 3 respectively, in which the total extra amounts of urine are 200 c.c. and 347.5 c.c. respectively. With this estimate there is a considerable allowance for error, for the figures for transudation from the skin are from a fairly high external temperature (without clothes), and it cannot be denied with the temperatures which the subject was exposed to in the present experiments that

¹ Scheierbeck's estimate, external temperature 30.4° C.

Experiment 4. March 8, 1906. Subject A. G. G. The legs were bound up as high as the knees in Esmarch's bandages for one hour. The subject remained in bed at rest throughout the experiment. The total urine produced in three hours was 378 c.c. The total extra urine was $378 - 140 = 238$ c.c.

Discussion of results.

It may be assumed as proved that a large amount of extra water is got rid of as the result of exposure to cold, but that the amounts vary according to the circumstances of the experiment. From the experiments in which the larger amounts of urine are produced (Nos. 2 and 3) it is necessary that another explanation be found than that which supposes the extra amount to be due to the deficiency in the loss of water vapour from the skin in consequence of vaso-constriction and lessened blood-supply to the skin; for, taking an average

more than a certain proportion of water loss by the skin was prevented by vasoconstriction. We may assume therefore that the body gives off water for reasons other than that it is merely a deviation of the evaporated water into the urinary channel.

It will be noticed in the figures representing the experiments that in those in which the excretion is largest, the maximum amount excreted occurs in the

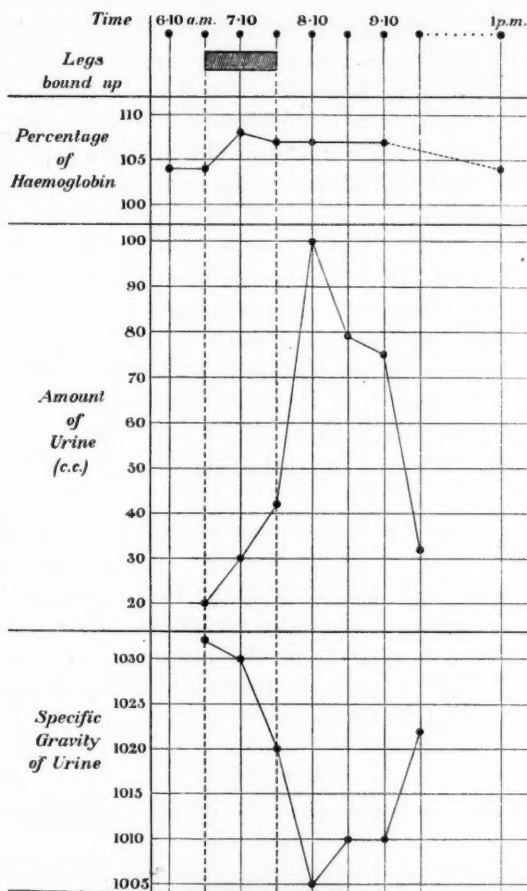


FIG. 7 (Exp. 4).

period of subjection to cold, whereas if the total amount was less the maximum was delayed, in the two experiments given (Experiments 5 and 6), for a period of $1\frac{1}{2}$ hours. The delay in excretion is almost certainly due to lessened intensity of the cold or to a shortening of the time of exposure.

As we should expect from the observation of the skin during exposure to cold, which becomes paler and shows the phenomenon of 'goose-skin' and constriction of cutaneous vessels, the blood pressure rises. The rise in maximum

blood pressure is immediate; indeed so sudden is it that although when records have been taken they have been made at the very beginning of the period, the readings have always been higher, sometimes very considerably higher, than the control observations before exposure. The rise of the minimum is neither so sudden nor so marked. Neither minimum nor maximum blood-pressure curve is parallel to the curve of excretion, especially when such is delayed so that the increased excretion is not directly the result of the alterations in the aortic blood pressure whatever the effect on the renal blood pressure.

The two experiments (Nos. 9 and 4) are confirmatory of the hypothesis that the increased secretion is due to an alteration in the distribution of blood in the body, for in Experiment 4, with no alteration in temperature of the body, bandaging the legs up to the knees in Esmarch's bandages was sufficient to cause 238 c.c. of urine to be secreted above the ordinary (calculated) amount for a similar period.

It may here be remarked that different subjects apparently react to different degrees on subjection to cold and after bandaging the limbs. Certain persons react with rapid and strong vaso-constriction and marked goose-skin even to moderate cold, while others show these reactions more slowly and in less degree. The effect of applying bandages to the legs depends upon the relative proportions of the legs to the rest of the body. In one subject (A. G. G.), in whom the rise of excretion after bandaging is most marked, the body is short and the legs stout, while in him (G. E. D.) who showed the lesser rise the legs are slim and the body tall.

The composition of the urine during the period of diuresis throws little further light on the nature of the diuresis. As has been said, in animal experiment haemoglobinuria, albuminuria, and even glycosuria are met with; but even under the severest cold of these experiments, as for instance in Experiment 3, no trace of any of these abnormal constituents could be detected. The only change detected by the ordinary tests was a tendency towards alkalinity of the urine at the height of the diuresis.

Conclusions.

1. A diuresis occurs as the result of chill which is too large to be more than partly accounted for by diminution of skin loss.
2. The diuresis attains its height during exposure when the cold is severe or the duration prolonged, but is delayed if the cold is not intense or the exposure short.
3. The variations in brachial blood pressure correspond to the exposure, but bear no close relation to the diuresis.

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TOXIC ARTHRITIS

By J. CAMPBELL McCLURE

THE two types of arthritis which I have chosen to discuss under the heading of 'Toxic Arthritis' are that which occurs after the injection of anti-toxic sera, and that 'rheumatic' form of arthritis which occurs in the course of scarlet fever and is not associated with oedema of the periarticular tissues or suppuration in the joint, but is characterized by periarticular swelling and thickening which is sometimes permanent and which may present some effusion into the joint of a purely serous kind, the affection which is commonly called 'scarlatinal arthritis'.

I have analysed for the purposes of this paper the cases of scarlet fever which occurred in the Glasgow Fever Hospital at Belvidere during the years 1901-1908, together with thirty others to which I was afforded access in private. The cases amounted to 170 in all, and of these 125, or 73.5 per cent., began in the first twelve days of the attack of scarlet fever, while the remainder were distributed over the other weeks of the disease up to the ninth week.

TABLE I.

OCCURRENCE OF SCARLATINAL ARTHRITIS DURING THE VARIOUS WEEK-PERIODS OF THE DISEASE.

In first week	56 cases
In second week	69 cases
In third week	10 cases
In fourth week	9 cases
In fifth week	11 cases
In sixth week	9 cases
In seventh week	4 cases
In eighth week	1 case
In ninth week	1 case
Total	<u>170 cases</u>

125 cases, or 73.5 %, occurred during the first fortnight.

The character and distribution of the arthritis varies somewhat according as it appears early or late in the attack of scarlet fever. In the 'early' cases a greater proportion of the smaller joints are involved than in the 'late', while in the late cases the larger joints are involved in greater degree than the smaller, although, as in all 'rheumatic' affections, it is usual to find more than one joint or set of joints attacked. Table II shows the percentage of one set of joints or another out of all joints affected in the various week-periods under consideration,

and it will be seen that as the arthritis falls later in the attack of scarlet fever there is a gradual increase in the percentage of the larger joints involved, while there is a corresponding decrease in the frequency with which the smaller joints are attacked.

TABLE II.

PROPORTIONATE INVOLVEMENT OF FINGERS AND WRISTS, ELBOWS AND KNEES IN VARIOUS WEEK-PERIODS, EXPRESSED IN PERCENTAGE OF ALL JOINTS ATTACKED.

	Fingers and Wrists	Elbows	Knees
In first week	47 %	19.65 %	11 %
In second week	37 %	17.00 %	17.00 %
In third week	29.5 %	17.65 %	23.53 %
In fourth week	20.00 %	20.00 %	33.33 %
In fifth week	23.00 %	14.30 %	28.6 %
In sixth week	15.33 %	15.38 %	30.77 %

The severity of the arthritis, also, varies a good deal with the time of its onset. The early cases tend to be more severe than the late, not only in respect of duration but in respect of acuteness, showing more frequently fluid effusion into the joints and being accompanied by higher fever and more severe pain. The cases occurring in the first fortnight of the attack of scarlet fever appear as a rule after a high initial pyrexia and other scarlatinal manifestations of the graver kind. The throat is usually acutely inflamed, and may indeed be of the anginous type, while there is frequently an early adenitis present in the cervical region. In many cases there is no defervescence of the temperature at a time when this might normally be expected to occur, while in others the usual lysis towards the end of the first week is not completed, but the curve is caught up again by an exacerbation, more or less severe, which is the accompaniment of the arthritis.

In 48 of the 125 cases which occurred in the first fortnight there was, besides the arthritis, one or other of the usual complications of scarlet fever, otitis media, cervical adenitis occurring about the time of normal defervescence, or an anginous condition of the throat with much sloughing and ulceration of the tonsils. There was no definite relation between the onset of the joint symptoms and the other complications in point of time. Many of the early cases suffered from severe myalgia during the course of the arthritis.

In the majority of the late cases, on the other hand, the initial attack was mild, terminating in a normal way without any other complication, and the arthritis was slight, accompanied by very little febrile disturbance. This slight constitutional disturbance was notable even in those cases where the arthritis lasted over a long time. The longest duration of a late case observed was twenty-four days, and in this case the knees and elbows were affected in a very mild degree; there was little pain or tenderness in the region of the joints, and the temperature never rose above 100° F. In three of the late cases, however, the arthritis was acute and severe and accompanied by high fever. In one of these, occurring in the fourth week after a very mild initial attack of scarlet fever, the joint

affection was associated with a severe otitis media which later gave rise to a mastoiditis for which a radical operation had to be performed. In the other two the arthritis was ushered in by the occurrence of a secondary tonsillitis, and one terminated fatally from cardiac failure, having developed a well-marked lesion of mitral incompetence during the attack of arthritis. In only one of the late cases was the initial fever severe and prolonged, and in this case the initial attack was complicated by the occurrence of an acute dry pleurisy which was present from the third to the twentieth day of illness.

As exceptions to the general rule that in the early cases of arthritis the initial attack is severe, may be quoted eighteen cases occurring during the first fortnight of the fever where the attack of scarlatina was very mild, with slight pyrexia and throat manifestations. In three of these cervical adenitis developed as a complication shortly after the beginning of the arthritis, and in one a mammary abscess occurred as a late complication. In this case the patient had been suckling a child until the onset of the scarlet fever. In the other fourteen cases no complication other than the arthritis was present, and none of the eighteen cases had prolonged or severe arthritic manifestations.

Only two out of the whole 170 cases observed ended fatally. One died on the twentieth day, having developed a cervical adenitis on the sixth day and a double otitis media on the fourteenth, the arthritis beginning on the eighth day. The other fatal case is the one previously mentioned, who died on the seventy-ninth day of illness, having developed a mitral lesion on the thirty-ninth day, the arthritis developing during the fifth week. This child took a secondary tonsillitis on the sixty-third day of illness, ushered in by an attack of vomiting which persisted until the child's death from cardiac failure. The urine was albuminous for a week before death, and on account of the degree of cardiac failure which existed it was deemed to be due to passive congestion, but the absence of a post-mortem examination makes any definite statement on this point impossible, and makes it also impossible to say whether or not the cardiac lesion was ulcerative in character.

Besides this case two others developed cardiac murmurs systolic in rhythm, heard best in the mitral area. In one of these cases, where the murmur was detected first on the twentieth day of illness, there was no doubt as to the cardiac defect being organic; but in the other, where the murmur was first heard on the eighth day, it was so faint and so definitely limited to the praecordium that there was reasonable doubt as to its having been of organic origin, the more so as the child was notably anaemic at the defervescence of the initial attack and remained so during the whole of his convalescence, while there was at no time any enlargement of the heart to be made out, and there was no accentuation of the pulmonic second sound.

The salicylates were used in the treatment of a certain number of the cases observed, but the results obtained by this form of treatment were not such as to be at all convincing as to its efficacy either for the relief of pain or for the cutting short of the attack. In no case could it be said that the pain was

definitely lessened by the use of the salicylates, and Table III shows the effect on the duration of the attack of arthritis.

TABLE III.

EFFECT OF THE ADMINISTRATION OF THE SALICYLATES IN SCARLATINAL ARTHRITIS ON THE DURATION OF THE ATTACK.

Those cases in which salicylates were given are called 'Treated Cases'.

Week	Total Cases	Average Duration	Shortest	Longest	Number of 'Treated Cases'	Average Duration	Shortest	Longest
1st	56	8 days	1	55	16	13 days	2	55
2nd	69	7 days	2	25	30	9.25 days	2	25
3rd	10	9 days	4	24	4	6 days	4	8
4th	9	6 days	3	11	4	6 days	3	10
5th	11	6.5 days	2	17	3	5.5 days	2	8
6th	9	7.5 days	3	24	2	13.5 days	3	24
7th	4	4.5 days	3	8	2	5.5 days	3	8
8th	1	4 days	—	—	0			
9th	1	3 days	—	—	1	3 days	—	—

A bacteriological examination was made in all cases where it was possible to do so, but unfortunately I was able to make such an examination in only 30 of the 170 cases observed. The method employed was the puncture of the affected joints and the withdrawal of what fluid was present, while at the same time 4 c.c. of blood were withdrawn from a vein in the arm, after laying it bare by an incision. In no case was a culture made from either blood or joints by piercing the skin with the needle of a syringe. The fluids to be examined were incubated in bouillon at 37° C., and subcultures were made on glycerine agar and blood serum. No antiseptic other than soap and spirit was used in the preparation of the seat of puncture, and all instruments were sterilized by boiling and used out of sterile water. Twenty-two of the cases examined were early cases occurring in the first fortnight of the disease, and in all of these the onset of the scarlet fever was severe, with marked throat affection. The other eight cases were late, occurring in the fourth, fifth, and sixth weeks of the disease, and in each instance the knee-joint was affected and fluid was withdrawn from the joint cavity itself or its synovial pouches.

The result of the bacteriological examination was similar in all cases. The blood cultures were sterile, and the only organisms which grew in the cultures made from the joints were, in one of the early cases, a few colonies of the staphylococcus albus and, in two of the late cases, a few colonies of a large coccus which was evidently a contamination.

Any attempt to draw final and definite conclusions from a limited number of bacteriological examinations which have yielded negative results is naturally subject to adverse criticism, and the number of cases examined in this series is admittedly too small to warrant any definite statement being made from these results alone. Moreover, although it would seem likely that the arthritis of scarlet fever is not due to the presence in the joints or periarticular tissues of

any of the known pyogenic organisms, such as the streptococcus group, the staphylococci, or the diplococci, it is possible that the arthritis, particularly the early arthritis, may be due to the presence in the joints of the causal agent of scarlet fever, and if this be, as seems possible, an organism higher in the developmental scale than the bacteria, it may be some time before it can be satisfactorily demonstrated whether there is a definite invasion of the articular tissues by an infecting organism, or whether the arthritis is produced by the toxins of some bacterium living remote from the joints and not infecting the general circulation.

But, in the meantime, there is a kind of arthritis recognized to be of purely toxic origin which offers many analogies with scarlatinal arthritis—that which follows the injection of any of the antitoxic sera derived from the horse. Here the arthritis is variable in severity, attacks mainly the smaller joints, is not accompanied by much effusion, but has an associated myalgia which is often very troublesome and, like scarlatinal arthritis, is not benefited by the use of the salicylates internally.

In the course of the first small epidemic of plague in Glasgow in 1900, certain of us who were then members of the resident staff at the Fever Hospital were injected with Yersin's anti-plague serum as a protective measure. We were unable to take any particular care of ourselves at the time, either in the way of rest or diet, and besides the common manifestations of serum-disease—urticaria, local and general, with some slight headache and nausea—four of us suffered, after incubation periods which varied from eight days to a fortnight, from moderately severe articular pain and swelling and, in one instance, from slight effusion into a joint. One of the visitors who came to study the epidemic, Professor Z. of St. Petersburg, had been repeatedly injected with a similar serum as a protection against plague, and presented a very typical multiple arthritis especially affecting the fingers and wrists. He stated definitely that until he had been injected with horse-serum he had never been subject to arthritis, nor was there any evidence of the arthritic diathesis in his family.

Such an arthritis is comparatively uncommon after the injection of serum for the cure of diphtheria, where the patient is strictly confined to bed and is on a limited dietary, while special attention is being paid to elimination, but I have had four cases under my observation at different times, and while two of the cases suffered only from slight pain and very moderate fever, in the other two the attack resembled in severity acute rheumatism. The onset was sudden and sharp, the joint-pains were acute, and the patients felt extremely ill. In one of the severe cases the attack ran a moderately sharp course for ten days and then rapidly subsided, but in the other, two relapses occurred after the first attack had passed off, and the patient did not recover from the effects of the serum until many weeks had elapsed. In none of these cases was the exhibition of the salicylates of any service in the alleviation of pain. It is quite common, however, to have some arthritis following the injection of anti-diphtheritic serum for purposes of prophylaxis, where patients are not at rest but are performing

their ordinary duties and on a full diet. In such cases those joints are particularly liable to be affected on which special strain is falling at the time, such as the wrists and fingers, shoulders or knees.

Various theories have been put forward to account for the occurrence of serum-disease, but the most likely hypothesis is that suggested by J. R. Currie in the *Journal of Hygiene*, 1907, where he suggests the possibility of the various symptoms of serum-disease, urticaria, arthritis, &c., being the result of the action of some particular antigen in the injected serum, which, combining with its antibody, produces a poison which under certain circumstances causes the symptoms. He supposes that in normal persons who are under conditions favourable for elimination the antibody is produced gradually, and the poison resulting from the interaction of antigen and antibody is also formed gradually, in such quantities as are easily eliminated by the organism without disturbance. In persons who show an abnormally quick response to the stimulation of the antigen, the poison may be produced in such quantity that it is beyond the immediate eliminative capacity of the individual, and an urticaria or an arthritis is the result, the tissues being attacked in proportion as they are most susceptible. Currie also discusses the possible methods of elimination of the poison which has been formed, but it matters little for the present purpose whether the poison is directly eliminated or is disposed of through the intervention of yet another antibody which it calls into being. What seems to me to be the important point in the hypothesis is that it explains how by the introduction of a toxic material which is bacterium free an arthritis or peri-arthritis may be produced.

It is possible, I think, to explain the occurrence of scarlatinal arthritis in the same way. It is an undoubted fact that in the majority of the early cases of scarlatinal arthritis the initial attack has been severe, but at the same time it is equally evident from the mortality-rate of the cases quoted that the patients are all capable of a good 'reaction' to the invading toxins. It is, therefore, credible that the early cases following on a severe initial attack may be due to the elaboration of a poison which is the result of the interaction of an antigen and antibody in such quantity that it cannot be rapidly eliminated by the organism and, remaining in the body, acts as an irritant on those tissues for which it has an affinity, the serous membranes of joints and the fibrous tissue which surrounds them. Similarly, in the early cases which occur in a mild attack of scarlet fever, while there is no excessive formation of poison, the amount produced may be too great for the eliminative powers of the individual, which are below normal, and a certain amount may be retained in the circulation and, fixing on the susceptible tissues, cause an arthritis. Again, those late cases unaccompanied by any other complication or re-infection may be accounted for in precisely the same way as the early cases which follow on a mild initial fever. We have evidence, in the relapsing cases of serum-arthritis, that antigen and antibody may go on producing poison for long periods, and this may occur also in scarlet fever, so that it only needs some influence to be

brought to bear on the patient which will lessen his eliminative capacity to provide all the materials necessary for the production of an arthritic attack. The late cases, which were ushered in by a secondary tonsillitis or some other infective complication, fall naturally into the same class as the early cases which follow an acute scarlatinal onset.

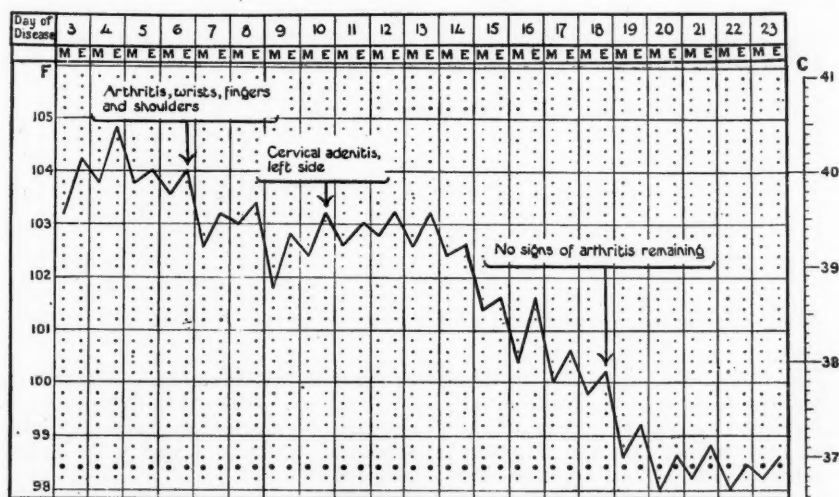
I append short clinical histories, with charts of the temperature, of cases which illustrate the main types of scarlatinal arthritis as described above.

Notes of Cases.

Case I. C. R., aged 12. Early case, with severe initial fever, much sloughing of tonsils, cervical adenitis, arthritis of fingers, wrists, and shoulders.

February 4, 1909. When seen this morning, on the third day of illness, the patient had a well-developed scarlatinal rash, the fever was high, and the tonsils were greatly enlarged, glazed, and red. There was a tendency to delirium and the patient was very restless. The urine presented a slight haze of albumin on boiling.

February 8. The patient had a very restless night, suffering much from pain in the hands, wrists, and shoulders. There was well-marked swelling



and redness of all the metacarpo-phalangeal joints of the right hand and phalangeal joints of the middle and index fingers. The right wrist was also greatly swollen and reddened, and the left shoulder was hot and painful and very tender to touch.

February 11. The joint-pains had been less severe, but this afternoon there was tenderness and enlargement of the cervical glands on the left side. The throat was much ulcerated.

February 14. The throat was cleaning satisfactorily and the cervical adenitis was almost gone. There was still some swelling of the affected joints of the right hand and the right wrist, but the shoulders were free from both pain and swelling.

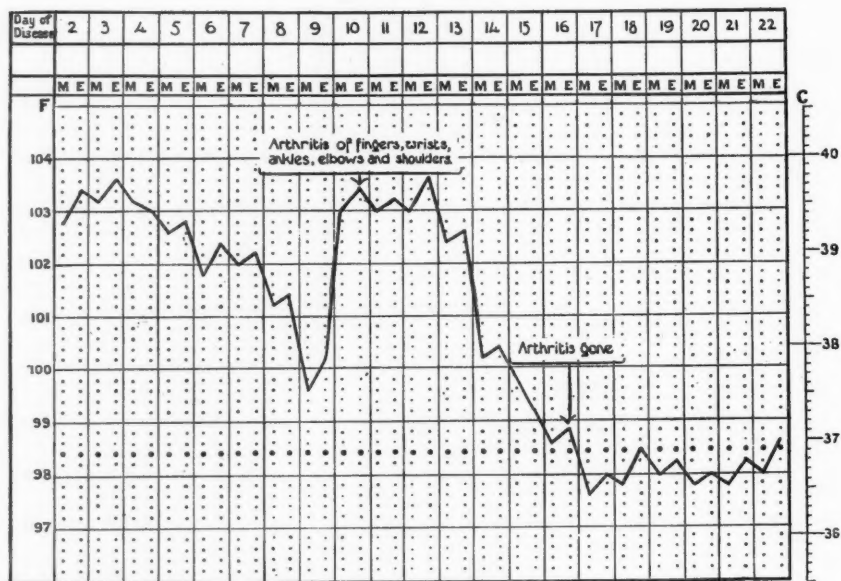
February 19. All signs of arthritis and of cervical adenitis had disappeared.

Case II. J. S., aged 17. Early case, with high initial fever and severe throat affection. Arthritis on the ninth day, towards the end of the lysis. No other complication.

December 18, 1908. When seen to-day, the second day of illness, patient was highly febrile and the tongue was thickly coated, while the tonsils were enlarged and reddened, with a good deal of exudate. There was a profuse and typical scarlatinal eruption. No albuminuria.

December 23. There had been much ulceration of tonsils and uvula, but the throat was looking cleaner, the skin was moister, and the fever more moderate.

December 29. On the morning of December 26 the temperature, which



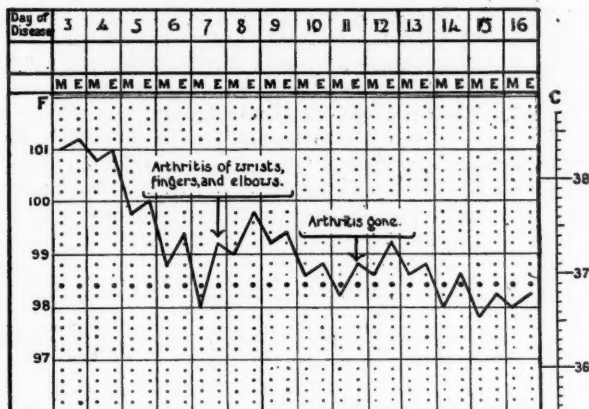
had been 100.2° F. on the previous evening, rose to 103°, and the patient complained of pains in the hands, ankles, and shoulders. Since then there had been marked swelling and redness of the phalangeal and metacarpo-phalangeal joints of both hands. Both wrists were also affected, and there was pain in both shoulders and elbows aggravated by movement.

January 2, 1909. All trace of arthritis was gone, and the patient felt perfectly well.

Case III. M. M., aged 16. Early case, with very mild initial attack and slight throat affection. Arthritis slight, affecting wrists, fingers, and elbows.

March 3, 1909. The patient had been ill since February 24 with a very mild attack of scarlet fever. The rash was well developed. The initial fever lasted only till March 1 and was very moderate. The previous day he complained of pain in the left wrist and fingers, and to-day he suffered in addition from pain in both elbows. There was quite a marked swelling of the first metacarpo-phalangeal joint of the right hand and the middle metacarpo-phalangeal joint of the same hand. Both wrists were also somewhat swollen, and there was pain on movement of both elbows.

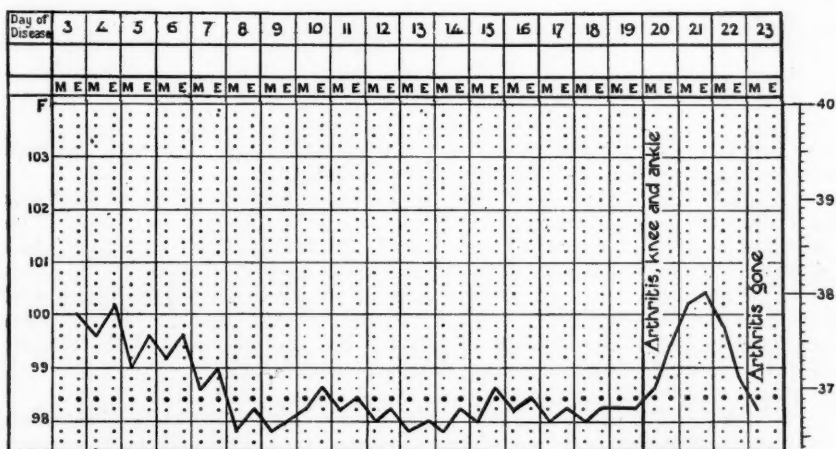
March 7. No signs of arthritis remained.



Case IV. Mrs. K., aged 20. A late case, with mild initial attack, and a slight arthritis on the twentieth day. The rash was well developed, and there was almost no throat implication.

September 8, 1908. A mild attack of scarlet fever with well-developed rash, slight enlargement of both tonsils, no adenitis, no albumin in the urine; it was the third day of illness. Temperature, 100° F.

September 26. Temperature fell to normal on the eighth day of the illness



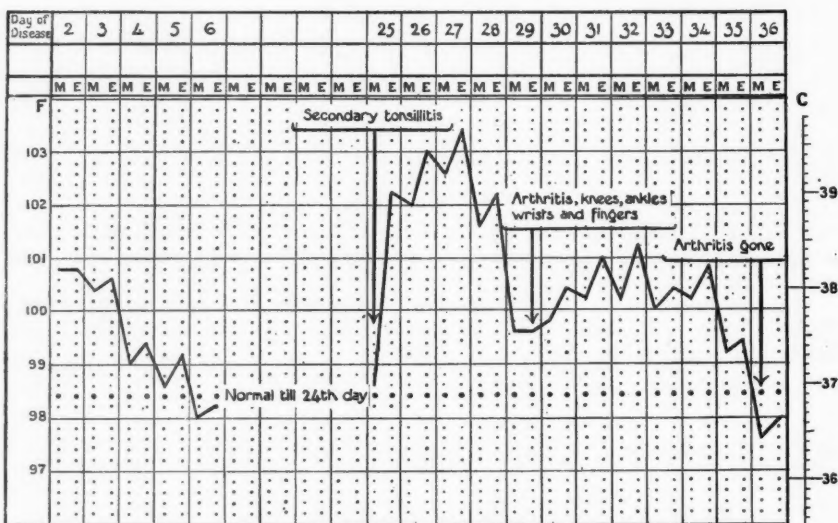
and remained so until last night, when it rose to 99.4°, and patient complained of pain in the left knee. A few hours later she complained of pain also in the right wrist. This evening the temperature was 100.2°, and both the right wrist and the left knee were swollen and tender, but there was no evidence of effusion into either joint.

September 29. The temperature reached normal yesterday and had not risen again. All signs of arthritis had disappeared and patient felt perfectly well.

Case V. W. N., aged 18. A late case, with mild initial attack; the temperature falling to normal on the sixth day, secondary tonsillitis on the twenty-fifth day, arthritis from twenty-ninth to thirty-sixth day.

March 8, 1909. Mild attack of scarlet fever, second day of illness. The rash was well developed; there was slight enlargement of both tonsils, and no adenitis was present. The urine contained no albumin.

April 1. The temperature fell to normal on the sixth day, and remained normal till yesterday evening, when it rose suddenly to 102.2° , and it was found that both tonsils were the subject of a severe follicular inflammation, and there was a little cervical adenitis present on both sides. This evening the tempera-



ture was 103° , and the patient was very restless and fretful. No rash had been observed in connexion with this secondary tonsillitis.

April 4. After three days' marked fever the temperature fell to 99.6° this morning. All pain had now left the throat and the tonsils were quiescent. The patient complained, however, of some pain in knees and ankles, and these joints were slightly swollen on both sides, but there was no fluid effusion.

April 11. On April 5 there was some effusion into the left knee-joint, and the wrists and fingers of the right hand were swollen and painful. The effusion lasted for three days. All signs of arthritis had disappeared and the patient felt perfectly well. The temperature was once more normal.

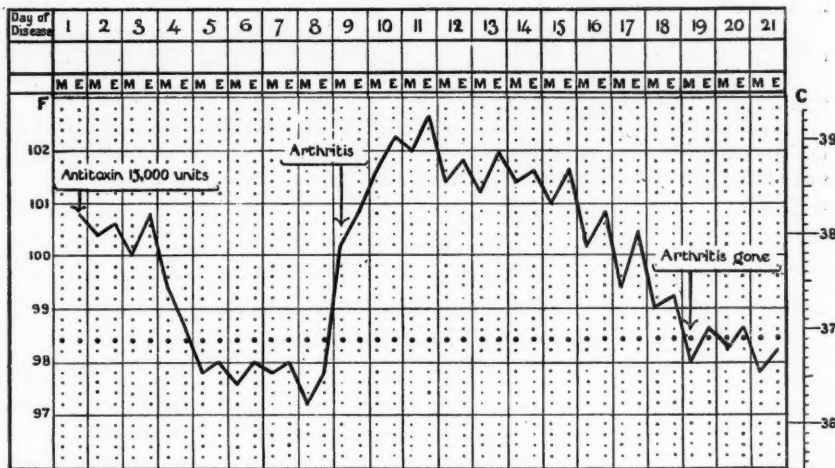
Case VI. Mrs. G. B., aged 27. Mild diphtheria. 15,000 units of antitoxin given on the first day of illness. Membrane gone on the third day, temperature normal on the fourth day. Severe arthritis affecting wrists and fingers of both hands and the right knee from the ninth to the eighteenth day of illness. Relapse from the twenty-third to the twenty-seventh day. Second relapse from the thirty-first to the thirty-seventh day. Thereafter a normal convalescence.

November 30, 1908. The patient suffered from a mild faucial diphtheria. Membrane on the left tonsil and tip of uvula. Right tonsil rather inflamed, but presenting no membrane. Temperature, 100.8° . 15,000 units of antitoxin given.

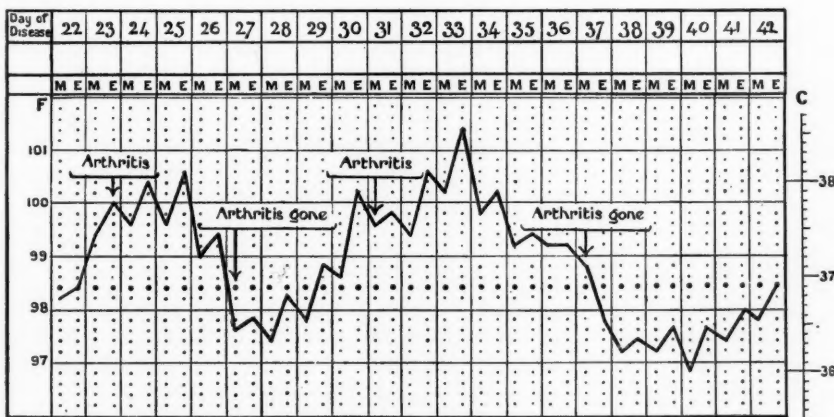
December 8. The membrane had disappeared on December 2, and the temperature was normal from the 3rd to the 7th. This morning it rose to 100.2° ,

and a few hours later the patient complained of acute pain in the right wrist and right knee. This evening the temperature was 100.8° , and there was pain and swelling of both wrists, all the metacarpo-phalangeal joints of both hands, and of the right knee. The pain was intense. Sodii salicylat. given in ten-grain doses every two hours.

December 10. During yesterday the temperature rose steadily, and this



evening it was 102.6° . There was no abatement in the pain and swelling in the joints, and the patient was inclined to be delirious. Sodii salicylat. reduced to ten grains every three hours.



December 18. Since the last note patient had become steadily better. As she complained of ringing in the ears the salicylate of soda was discontinued on the 11th; it had no apparent effect on the pain, which had to be relieved by morphia. From the 14th the temperature steadily declined until this

morning it was normal, and the pain and swelling in the joints had gradually disappeared.

December 22. The temperature remained normal since the last note until this morning, when it rose to 99.4° , and this evening it was 100° . The patient complained of pain in the right knee, which was distinctly swollen and slightly reddened.

December 26. The temperature had once more reached normal, and the pain and swelling in the right knee were gone.

December 30. For the past twenty-four hours the temperature had been slightly febrile, and this morning there was distinct swelling, pain, and tenderness in the left wrist, while the first right metacarpo-phalangeal joint was also swollen, red, and acutely painful.

January 8, 1909. The temperature had been normal since the 5th, and by that day also all signs of arthritis had passed away. Patient did not suffer from even the slightest stiffness in the joints and felt quite well.

SOME OBSERVATIONS ON THE ORAL ADMINISTRATION OF T.R. TUBERCULIN IN PULMONARY TUBERCULOSIS

BY DAVID LAWSON AND H. S. GETTINGS

IN Copeman's work it is recorded that as far back as 1810 the administration of the contents of vesicles to a girl by the mouth was followed by the appearance of a typical variola eruption, thereby demonstrating the fact that it is possible to obtain a reaction by orally administering a vaccine. When Koch produced his tuberculin he definitely stated that administered orally it was inert, and so great was the influence wielded by that great pathologist that for many years no one appears to have questioned his assertion. It was not till Hort in 1907, in an article published in the *Lancet* in December of that year, claimed to have administered vaccines and tuberculins by the mouth successfully that the point began again to receive consideration. His work appears to have stimulated the imagination of Latham, for we find within six months a preliminary communication dealing with work done in association with Spitta on the oral administration of horse-serum appearing in the *Transactions of the Royal Society of Medicine*. Again, at a later date we find in the *Transactions* of the same Society two papers by Latham and Inman dealing with the same subject. The last paper in particular is one of extreme value and importance, not only on account of the extensive nature of the research, but also because of the conclusions at which the observers have arrived. The two conclusions which concern us in this paper are:—

1. T.R. Tuberculin administered orally exerts a definite influence on tubercular disease.
2. The action so exerted bears a constant relationship to the patient's temperature, and that relationship is an inverse one.

It appeared to the writers a matter of great importance that further evidence should be brought to bear upon the question whether or not tuberculin may be effectively administered by the mouth in cases of suspected or actual tubercular disease. If it were so, then the following advantages would accrue:—

1. The nervous patient would be saved the feelings of dread with which he is accustomed to contemplate the employment of the hypodermic needle.
2. Where an attempt is being made to secure passive immunization, and therefore where larger doses of serum are involved, it is more practicable to administer such a quantity of serum orally than hypodermically.
3. A saving in time and trouble to the doctor in general practice can be

achieved, for the personal attendance essential when a hypodermic needle is used may be dispensed with when the serum has to be swallowed.

4. If, as is claimed, the temperature is a reliable guide in regard to a reaction caused by the administration of tuberculin, then no longer need we trouble our patients with systematic opsonic estimations. The patient would thus be saved the irritating procedure of having samples of his blood withdrawn, and further, the very heavy expense avoided which is entailed by systematic blood estimations as at present carried out. This would lead to the further extension in general practice of the employment of vaccine treatment if its administration were no longer hampered by its association with the difficult, expensive, complex, and not always reliable procedure involved in systematic opsonic control.

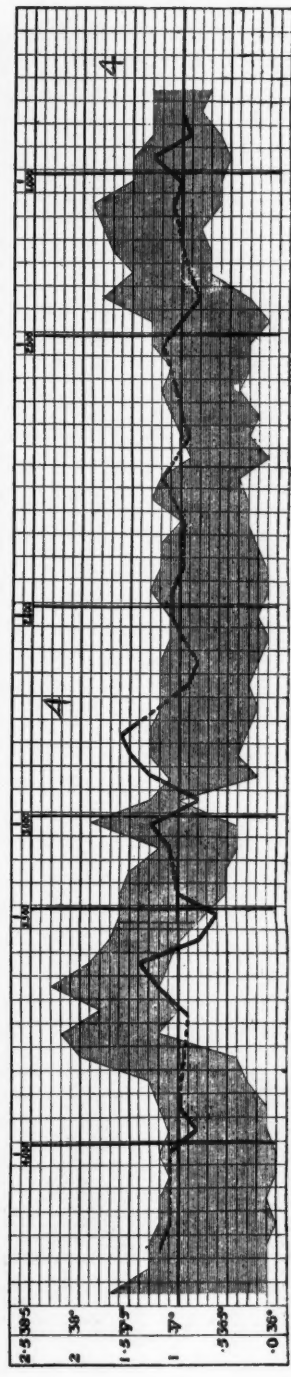
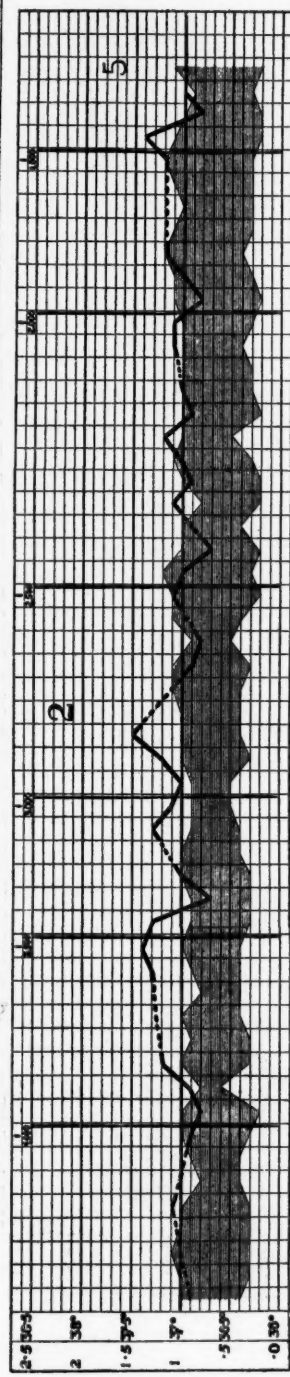
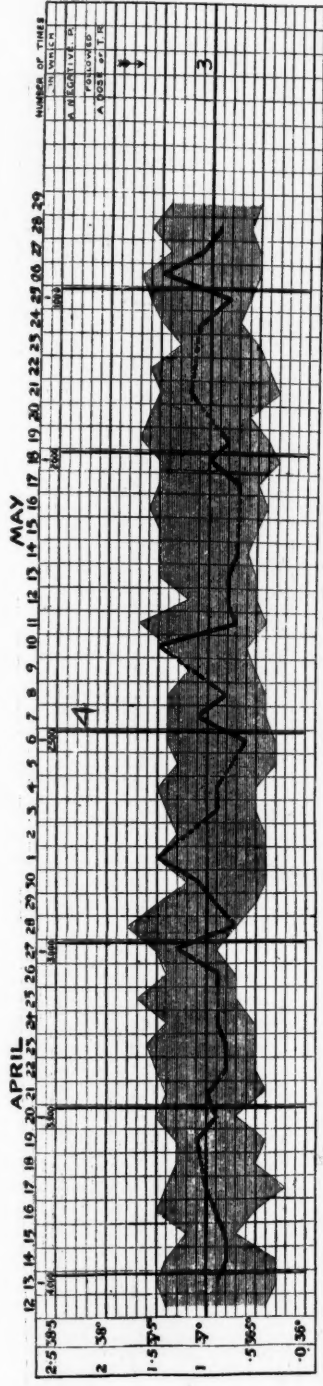
There was still one further reason which prompted us to undertake this inquiry, a reason of a personal nature. For the conclusion arrived at was at variance with that which one of us working in association with Dr. Struthers Stewart was led to adopt, as the result of an inquiry into the relationship of the negative phase to the body temperature made in 1904 and recorded in the *Transactions of the Royal Medico-Chirurgical Society* of that year.

We therefore selected six cases of pulmonary tuberculosis; four of these were apyrexial and two were pyrexial. All were cases of somewhat extensive disease, and all were more or less old-standing. Full clinical records were kept embodying observations on the pulse, respiration, temperature, weight, and urine. We are not able to base any conclusion on some of those records, and so far as they seemed to have no bearing on our ultimate conclusions these have been eliminated. Only those parts of the record essential for our purpose have been retained in the charts prepared. The blood of each patient was taken every morning before breakfast and subjected to the ordinary opsonic test. The doses of tuberculin were given at 10 p.m., when presumably the patient's stomach was empty.

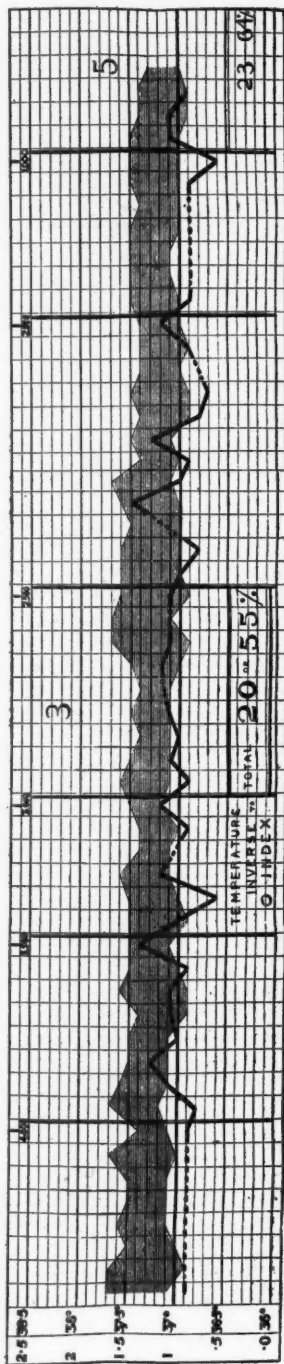
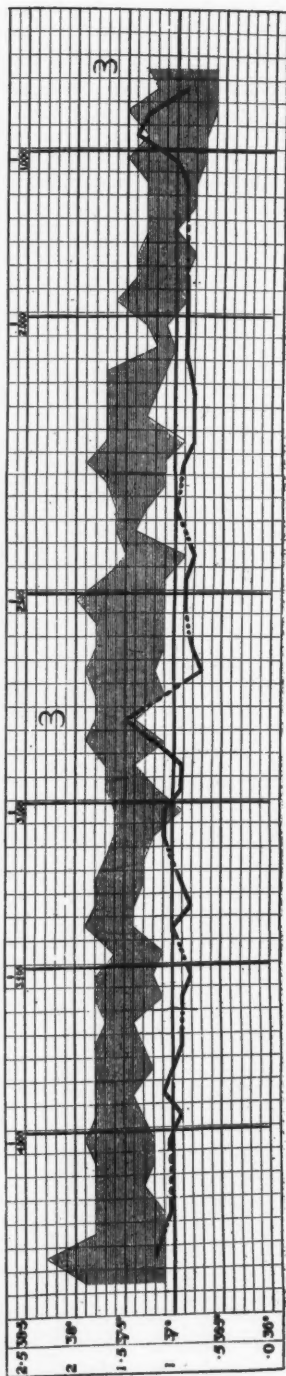
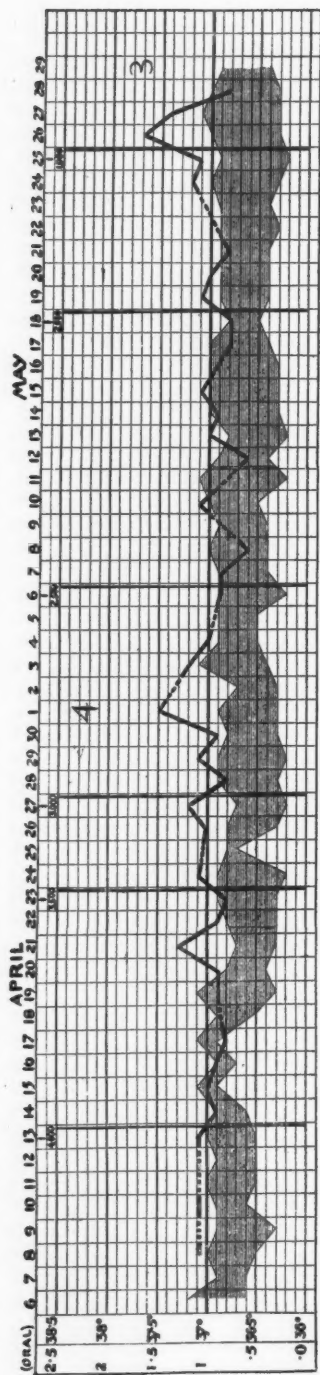
Certain precautions were taken to eliminate the more apparent sources of error. To obviate the personal factor measures were adopted to prevent the observer being aware whose blood he was dealing with until the close of the experiment. To effect this the blood capsules, both of control and of patient, were handed to him merely bearing numbers, and it was not until the completion of the counting that he was made aware of the identity of each blood.

Secondly, in regard to technique, the earlier standard of counting 50, or even less, polynuclear cells is now recognized as not sufficiently reliable, and therefore throughout the inquiry a minimum of 100 cells was adopted. In this way over 28,000 cells were examined in the course of the research.

Further, it had been previously recognized that when the bloods were incubated in batches, withdrawn at the same time, filmed and stained seriatim, the cells of those last prepared showed a uniformly larger proportion of bacilli than those done first. This is due to the phagocytosis that evidently still goes on at room temperature during the interval of waiting.



Pressure & Temperature Logarithm



It occurred to one of us that probably if the leucocytes were chilled such phagocytosis might be stopped. Accordingly on withdrawing the pipettes from the incubator they were at once placed in a vessel of cold water and taken out one by one as required. We think that this method gave us increased accuracy in our results, and we desire to draw the attention of fellow workers to this point.

A study of the charts will now reveal the basis of the conclusions at which we have arrived, and the ground upon which they are based. The charts have been drawn out in such a way as to show (1) an opsonic curve, indicated by a single line; (2) the altitude of the daily range of temperature, indicated by shading in the space enclosed by the curves, got respectively by joining the highest points and the lowest points recorded each day; (3) the doses of tuberculin and the dates on which they were administered by mouth, indicated by vertical lines. In comparing the relationship of the opsonic curve to the temperature curve it should be noticed that the lower of the two temperature curves indicates that obtained each morning at 8 a.m. before any factors have intervened to disturb it. As 8 a.m. also corresponds to the time at which the blood was withdrawn from the patient, it has been considered desirable to employ it in preference to that indicating the higher range. Let us then ask two questions and ascertain what answers, if any, the charts supply to them.

In the first place:—Can tuberculin when given by the mouth exert an action on the blood content as indicated in the variation of the opsonic index in a person suffering from tuberculous disease? Out of the thirty-six instances in which doses of tuberculin varying in amount from $\frac{1}{4000}$ to $\frac{1}{1000}$ mg. were administered, in twenty-three instances (or 64 per cent. of the whole number) a negative phase immediately appeared. The fact that in 64 per cent. of the occasions referred to a definite negative phase was recorded seems to support the claim made by Latham and his colleagues that tuberculin administered by the mouth in cases of tuberculosis is absorbed and modifies the blood content.

In the second place:—Is the inverse relationship of the temperature curve to that of the opsonic index so constant that the latter, and therefore the varying resistance of the patient to tuberculous disease, may be safely inferred from the former? In the charts shown here are instances in which a rise of temperature taking place contemporaneously with the fall of the opsonic index curve is very striking. These amount in all to twenty, or 55 per cent. of the whole number. After, however, allowing for the smallness of the number of observations and for other obvious sources of fallacy, we do not think that the 55 per cent. arrived at warrants the conclusion that the temperature is a safe and reliable guide as to the behaviour of tuberculin in the body.

SOME FURTHER REMARKS ON LEUKAEMIC AND CHLOROMATOUS AFFECTIONS

By C. H. TREADGOLD

SINCE my previous communication only four cases of chloroma seem to have been reported. Two of them were described in great detail.

Case I. (Reported by Fabian.) Woman, aged 45. Always suffered from tendency to anaemia. Feeling of fatigue and exhaustion dating from January, 1905. This got worse till in August the author was consulted. On examination, nothing found. No enlargement of liver, spleen, or glands.

October 9. Extreme fatigue. Tonsils somewhat enlarged.

November 20. Palpable glands below angle of right jaw, also at nape of neck. Small hard nodules noticed in the skin of back and limbs; these gradually increased to the size of peas.

November 28. Increased pallor. Spleen a little enlarged. Increase in size of glands below angle of jaw.

December 6. Tonsils not enlarged.

December 12. From this point onwards irregular pyrexia. Increase in size of spleen and tonsils. Enlargement of glands in neck and groin. Increased anaemia. Continual headache necessitating morphia.

December 19. Glands below angle of jaw larger, spleen larger, cutaneous nodules about the same. Haemorrhage from tonsil.

December 20. Death took place.

Treatment. Arsenic and iron throughout.

Results of blood examination.

	Aug. 4.	Nov. 3.	Nov. 13.	Dec. 18.	Dec. 19.
Red corpuscles	Slight anaemia.	3,360,000	2,020,000	800,000	Condition of blood about the same.
White corpuscles	Leucocytic count not increased.	8,000	6,000	220,000	
Large mono-nuclears	69%	73%	35%	61%	
Intermediate forms	—	—	9%	—	
Lymphocytes	10%	14%	Rather larger lymphocytes, 50%	14%	
Polymorphs	21%	13%	7%	4%	
Mast cells	—	—	3%	—	
Myelocytes	—	—	A few	—	

From November 3 onwards many of the white cells showed marked degenerative changes.

(Q. J. M., Oct., 1909.)

Post mortem. Cutaneous lymphomata. Varied from pea to cherry in size, green on section. Spleen and liver enlarged. Mesenteric glands enlarged and greenish. Small greenish yellow points all over kidneys. Thymus enlarged, colour greenish yellow. Tonsils as large as plums, and greenish. Submaxillary glands enlarged and greyish green. Marrow of sternum, femur, and rib greyish red.

Smears from liver, spleen, kidney, thymus, and marrow of femur showed enormous numbers of large, non-granular mononuclear cells. These cells varied from twice to three or even four times the size of a normocyte.

Sections showed a similar appearance in marrow, thymus, tonsils, spleen, kidney, caecum, skin nodules, and pancreas. The thyroid, heart muscle, suprarenals, lungs, and uterus showed a large increase of these cells in the vessels. The liver capillaries were dilated and filled principally with large mononuclears. In the intra-acinous connective tissue were numerous round patches consisting chiefly of large non-granular mononuclear cells. Typical marrow giant cells in thymus and tonsils, and to a less extent in the spleen and nodules of the kidney. The author says little about the etiology and nothing about the seat of primary disease, but contents himself with remarking that 'whether the condition is a pure hyperplasia or an atypical proliferation analogous to the malignant tumours needs solution'.

Comments. The age of the patient and the duration of the disease (nearly 12 months) are noteworthy features. Had the bones been more extensively investigated general involvement of the marrow would almost certainly have been found, and possibly green marrow with periosteal or subperiosteal deposits somewhere or other. The case is a beautiful example of primary affection of the bone marrow, localized at first, but gradually becoming generalized as shown by the slowly progressive anaemia. Towards the end the disease broke all bounds, as shown by the rapidly increasing anaemia and the large number of white cells in the blood which became generally distributed all over the body.

The late enlargement of the glands and spleen is interesting, and proves them to have been only secondarily involved. That the spleen does not become markedly enlarged in those cases in which only a small number of marrow cells appear in the blood is also well illustrated.

Case II. (Reported by Havilland Hall.) Girl, aged 4, admitted November 8. One month before admission child became irritable and complained of headache. This increased in severity and kept her awake at night. A fortnight before admission prominence of the eyes was noticed, also a lump on each side of neck and distension of veins over the temporal region, which was more marked on the right side. On admission the condition was substantially the same. Nothing else was found.

November 12. Double optic neuritis. Both swellings distinctly larger and veins more prominent.

From November 24 onwards the swellings diminished somewhat; the appetite increased and patient put on weight, although the anaemia grew more marked.

During the last week of the illness the temperature was 'swinging' in type. A prolonged attack of epistaxis occurred on December 19.

December 24. Death took place.

Results of blood examination:—

	Nov. 9.	Nov. 16.	Nov. 30.	Dec. 7.	Dec. 23.
Red corpuscles	4,100,000	3,710,000	1,690,000	1,612,500	1,140,000
White corpuscles	40,600	38,400	37,400	27,100	23,900
Large mononuclears	65 %	66 %	66 %	35 %	19 %
Intermediate	3 %	—	5 %	6 %	6 %
Lymphocytes	17 %	17 %	22 %	30 %	19 %
Polymorphs	15 %	17 %	7 %	21 %	44 %

Treatment. Liquor arsenicalis in three-minim doses, afterwards increased to five minims three times a day in combination with citrate of iron and ammonia.

Post mortem. Green growth in temporal and parotid regions. On removing the skull-cap and brain a similar growth was seen in the ethmoidal region, middle fossa, orbits, and dura of vertex. In the trunk, chloromatous tissue was found on the internal aspect of all the ribs, the innominate bones and sacrum, and on the external surface of both scapulae. The long bones (one examined) appeared exempt. All the growths were olive green in colour and periosteal in situation.

Microscopical examination showed a small to medium sized round-cell sarcoma. In the fresh state the cytoplasm of many cells was of a greenish hue, homogeneous, and oily looking. After section, &c., it became granular and yellow and recognizable with difficulty. Notwithstanding the red appearance of the bone marrow at the time of the autopsy, the presence of pigmented cells was demonstrated in unstained specimens and also in the spleen.

Comments. This case is a good example of what is supposed to be typical chloroma. Hebb and Bernstein, who conducted the pathological investigation, describe the growths as sarcomata and incline to the view (not unnaturally from a consideration of their case) that chloroma is a disease *sui generis* and not closely related to leukaemia. Hall says, 'Although a considerable increase in the leucocytes was present, it does not approach anything like the number met with in a severe case of leukaemia.' Yet I myself have seen three cases of acute leukaemia in none of which did the highest count reach 30,000 white cells per c.mm.! In this case over 40,000 white cells per c.mm. were present on admission.

The administration of arsenic tends to prevent these cells from increasing in the blood, as will be shown later. The continuous administration of arsenic seems, in Fabian's case, to have kept the disease under control and to have prevented the blood from becoming markedly involved for a considerable period. In Hall's case the cells seem to have been of a rather more primitive type. However, it must be remembered that smears were not made in this case and that degenerative changes, which are frequently present (cf. Fabian's case), make the cells appear much larger than they really are; also that the process of hardening tissue makes the cells appear smaller. The other two cases were briefly reported and the condition was not suspected before the autopsy.

Case III. (Reported by Port and Schütz.) Male, aged 16. Admitted January 7, 1907. Very anaemic; showed a petechial rash and complained of epistaxis.

February 8. Vomiting and melaena.

Examination of blood:—

Red corpuscles	740,000 per c.mm.
White corpuscles	44,000 per c.mm.

The principal cells were large mononuclears.

Post mortem. The inner surface of the skull-cap was of a greenish grey colour. The bronchial glands and the glands at the bifurcation of the trachea were enlarged and greenish.

Microscopical examination. The marrow examined was composed of myelocytes and large mononuclear cells.

Case IV. (Also reported by Fabian.) Male, aet. 31. Admitted February 20, 1907, for struma maligna. The chief things noticed were a large mass of glands along the right sterno-mastoid, and anaemia. The anaemia gradually increased in severity and the glands in size.

June 28. Death took place.

Post mortem. On removing the skull-cap greenish diploë was noticed. Numerous greenish nodules were present in the dura mater. There was periosteal thickening over the posterior surface of the sternum and greenish yellow nodules were seen in it. Similar periosteal swellings were present on some of the ribs. The axillary and cervical glands and those in the portal fissure were enlarged and of a light green colour. The thymus was absent. The liver and spleen contained numerous nodules of a whitish or yellowish colour. Numerous yellowish green nodules were present in the yellowish red to deep red marrow of the femur, sternum, ribs, and lumbar vertebrae. The other vertebrae showed a yellowish green marrow. Microscopical examination showed the condition to be a chloroleukaemia of a myeloid character. Smears from the marrow showed a predominance of white cells, including neutrophil and eosinophil myelocytes, myeloblasts, and plasma cells; also a few mast cells and nucleated red corpuscles.

All four cases seem to have originated in an atypical proliferation of the cells which normally produce myelocytes, that is to say, the pre-myelocytes or myeloblasts. Clinically, all four cases showed at some period or other a marked resemblance to acute leukaemia, although this was rather less marked in Hall's case, in which the cells seem to have been of a slightly more primitive type. In this case the absolute number of polymorphs in the blood remained about normal, suggesting a more local affection of the marrow than was present in the other cases. However, the marrow seems to have been extensively affected in all of them. In my opinion, therefore, all four cases support the view that the marrow is primarily affected in chloroma and that the condition is closely allied to leukaemia. (I have dealt more fully with this point in this Journal, 1908, i. 239.)

Within the same period some interesting cases of acute leukaemia have been reported. Emerson enriches the literature by describing another case of acute leukaemia in which the vertebrae only were involved. He says, 'Had the pathologist stopped in this case with the examination of the ribs and femur, the case could have been reported as acute lymphatic leukaemia without bone marrow lesion.' Forbes and Langmead collected twelve cases of acute lymphocythaemia in early life, of which the microscopical appearance of the marrow was detailed in two.

Case I. Male, aged 2. Apparent duration of illness, one month. Glands only enlarged in region of sterno-mastoid, one being a little larger than a pea. Spleen enlarged. No oral sepsis.

Examination of blood showed:—

Large lymphocytes	:	:	:	:	:	84 per cent.
Small lymphocytes	:	:	:	:	:	14 per cent.

Microscopical examination. Marrow. It was calculated that not more than one in 10,000 cells was other than a lymphocyte. In the spleen no definite changes, apart from an excessive number of lymphocytes in the blood, could be seen. The gland examined showed an excessive number of lymphocytes and an absence of germinal centres. The liver and kidneys showed what appeared to be badly formed adenoid tissue without germinal centres.

Case II. Female, aged 7 months. Apparent duration of illness, one week, but pale since birth. No oral sepsis.

Large lymphocytes	:	:	:	:	:	65.7 per cent.
Small lymphocytes	:	:	:	:	:	33.4 per cent.

Post mortem. Liver, spleen, kidneys, and superficial glands enlarged; deep-seated glands not affected.

Microscopical examination. Films from bone marrow showed the cells to be nearly all large lymphocytes; same condition found in films from kidney, liver, spleen, and subcutaneous blood effusions.

Synopsis of twelve cases. In every case the blood condition showed marked anaemia. In seven cases the red corpuscles numbered under 1,500,000 per c.mm. before death. In six cases under observation for a period of from four to six weeks, a steady fall in the number of red corpuscles was traced during the later stages. Blood films from all cases showed an excessive number of non-granular cells, both large and small, almost entirely replacing the normal cells. Glandular enlargement was absent in one case. In four cases the glands were slightly enlarged in some situations. In the other cases glandular enlargement was more general, though never very marked. The liver was almost invariably enlarged. In all cases collections of lymphocytes were found underlying the capsule, and the connective tissue enclosing the portal canals was the invariable seat of lymphocytic invasion.

The spleen was usually enlarged. Microscopically the pulp was congested and crowded with lymphocytes; but these cells were usually more obvious round the Malpighian bodies, investing the blood-vessels in the form of a sheath, thus denoting involvement of the perivascular lymphatics. In nine out of twelve cases there was general lymphocytic invasion of the kidneys, most marked in the cortex. This was often so extreme as to leave scarcely any normal tissue intact. In one case the kidney examined was almost completely replaced by lymphocytes, only scattered islets of glomeruli and tubules remaining. (It is to be noticed that the authors use the term 'lymphocyte' in its widest sense.)

In the remainder of this paper I propose to deal first with some further evidence as to the origin of the cells and the seat of primary involvement in leukaemia, and secondly to give a detailed discussion of the pathogeny of leukaemia and allied affections. It is interesting to note that Dickson, in his recently published monograph on the marrow, for which he prepared and

examined over 4,000 microscopical specimens, gives a genealogical tree for the different blood-cells almost identical with the classification given in my previous paper, but worked out from the examination of normal marrow. He prefaces his remarks by pointing out that 'the more obvious mechanical functions which the osseous system has to perform have masked and in great part prevented due attention from being bestowed upon the other equally if not more vital rôle which this tissue has to play—that of producing the great majority of the formed elements of the blood. That so far from being unchanging in their structure, the bones, with the exception of the blood itself, are the most unstable tissue in the body, and alterations may be produced with the most remarkable rapidity not only in the marrow but also in the hard and apparently unyielding osseous portions proper.' That this statement holds, at any rate as regards the marrow, goes without saying. I can recall a case (not mentioned in my previous paper) in which extensive intrathoracic growth was associated with lymphomata in the kidneys and marked leukaemia. The marrow was markedly affected and showed few red cells, yet the red-cell count was 5,000,000 c.mm. shortly before death. Clinically the case was very acute, about a month. The pathogenic cells were similar in the blood, marrow, and growth, and resembled the large-cell type of acute leukaemia. In this case the primary lesion must have been focal, the marrow only becoming extensively involved a few days before death; moreover the pathogenic cells must have proliferated at a tremendous rate for the marrow to have been so extensively affected without anaemia.

Dickson regards the undifferentiated lymphocyte (Wolff) as the parent cell of the pre-myelocyte and myelocyte series, and also of the differentiated lymphocytes which are present in normal marrow. He states that the undifferentiated lymphocytes are larger than the differentiated, and react somewhat differently to stains, and that in normal human marrow all gradations are present between pre-myelocytes and undifferentiated lymphocytes. He says that in normal marrow ordinary lymphocytes are scattered irregularly among the other cells, and are sometimes aggregated into small areas closely resembling the structure of lymphoid tissue elsewhere, the cells lying in the meshes of a definite adenoid reticulum.

It is a fact that after birth the marrow produces the red corpuscles and all kinds of leucocytes, and that the glands and spleen produce lymphocytes, some of which make their way into the blood, although the glands are intercalated in the lymph-stream in such a way as to make it difficult for the lymphocytes they produce to get into the blood. The spleen is practically a lymph-gland interposed in the blood-stream, so that its cellular details and scaffolding have necessitated modification on this very account. The marrow is the great factory for the production of blood-cells, and, being protected by a bony covering in a veritable backwater of the circulation, requires very little specialization to prevent too free a contribution of cells to the blood (Batty Shaw). The marrow produces the cells which take an active part in the destruction of

organisms, the lymphadenoid tissue being more directly concerned in dealing with the toxins produced by those organisms, while the spleen in addition helps to sort out effete material from the blood. Thus the matter lies in a nutshell. In lymphosarcoma, lymphadenoma, lymphoma, and other affections of obscure nature which sometimes involve the glands and spleen, the white cells of the blood are very seldom affected, but, *per contra*, when the marrow is involved these cells are almost always affected. It is thus very evident how weak is the mechanism for preventing the escape of cells from the marrow to the blood when compared with that of the glands and spleen, thus indirectly proving how large a proportion of blood-cells is furnished by the marrow, the cells under conditions other than leukaemic being produced only as they are wanted. Such being the facts, it should not be difficult to explain the varying forms of non-granular leukaemia. The large-cell non-granular leukaemia which usually occurs in early life probably corresponds to the chronic myelocythaemia of adults. That is to say, cases of so-called acute lymphatic leukaemia are really acute myelogenous. What is at the present time termed acute myelogenous leukaemia would appear to be an almost identical condition, the only difference being that a varying proportion of cells become sufficiently differentiated to form granules. Chronic lymphocythaemia appears in many (perhaps all) cases to be due to the involvement of the marrow lymphocytes, and corresponds in age incidence with chronic myelocythaemia. The acute small-cell lymphocythaemia which sometimes occurs in early life forms the rarest variety of the four types under consideration, and would dovetail into the general scheme by supposing the lymphocytes of the marrow and their ancestral forms to be implicated. As a general hypothesis there is much to be said in favour of this scheme; e.g. chronic myelogenous leukaemia occurs more frequently than chronic lymphatic leukaemia. Similarly, acute large-cell leukaemia (acute myelogenous) occurs more frequently than the acute small-cell form, as we should expect. For more direct evidence as to the primary affection of the marrow in acute leukaemia my previous paper should be consulted.

Now a word with regard to the origin of the cells in chronic myelocythaemia. The granulocytic deposits found in the various organs are now very generally held to originate in the marrow. Some of the proofs that this is so are perhaps worth mentioning.

(i) The occurrence of leukaemia for all practical purposes denotes an affection of the marrow.

(ii) The analogy with acute leukaemia and the fact that chronic cases sometimes change into acute.

(iii) The fact that the production of granulocytes is, at any rate after birth, confined to the marrow.

(iv) Microscopical examination shows that in the marrow myelocytes are very plentiful and in active process of division; large mononuclears and characteristic giant cells are also fairly plentiful.

The spleen contains polymorphs, myelocytes, and cells intermediate between

the two; non-granular mononuclears are rare, while giant cells of the marrow type are usually fairly common.

(v) Granulocytes are frequently present in the liver, kidneys, and glands, and marrow giant cells are usually present also.

(vi) The alteration in the blood is the first sign of the disease, the spleen, liver, &c., becoming enlarged coincidently with the increased number of white cells in the blood. These organs appear to play the part of filters; e.g. the liver capillaries become distended with these cells, and in time absorption of the capillary walls takes place owing to pressure.

Of course in so controversial a subject as leukaemia it is only right to say that there are authors who dissent from some of these views. For example, Cabot (in Osler and McCrae's *System*) supports the old idea that the whole haemopoietic system—marrow, spleen, and lymph-glands—is involved in every case of leukaemia, and that it is not sharply differentiated into myeloid and lymphoid elements. He argues that in chronic myelocythaemia the glands and spleen undergo myeloid transformation, thus reverting to a less specialized type of cell, and considers this explanation to be more in harmony with the facts than any theory of transplantation of marrow cells into glands, or gland cells into the marrow.

He quotes the lymphoid transformation of the marrow in acute leukaemia and the fact that the glands and spleen are not enlarged in some of these cases as supporting this view. Yet the balance of evidence would seem to be overwhelmingly against it.

In the first place, as Michell Clarke points out, the transplantation of lymphocytes into the marrow is not in question, as it always contains them; moreover no one seems to have suggested the likelihood of such an occurrence. Yet the converse is a very different matter, for it has been proved that marrow cells are transported to the spleen, glands, &c., in leukaemia. Moreover, if glandular and splenic tissues were capable of reverting to granulocyte formation (which incidentally they are unable to do owing to the granulocyte being a more specialized type than the lymphocyte), we should expect a myeloid glandular condition to occur in children, since a reversion to a less specialized type in them so easily occurs. But we know that no such condition exists. If we pursue his hypothesis any further we are reduced to imagining the glands and spleen, although unable to assist the marrow by producing granulocytes in known infective disorders, yet ready and willing to produce a more differentiated type of cell than they have ever done before when there is a superabundance of such cells in the system already. Such an idea is quite untenable, and can only have arisen from a belief in the old view which it is so hard to dispel—namely, that the non-granular marrow cells are identical both in function and structure with the gland lymphocytes.

The etiology of the leukaemias.

I shall first endeavour to show how unlikely it is that an infective process plays anything more than an indirect part in the causation of these affections. I know that some authors claim the leukaemias to be conditions in which the characteristic blood changes are brought about as a specific defensive reaction of the marrow, having as its main object the protection of the organism and the destruction of the hostile substances invading it, that it is a specialized form of leucocytosis (Dickson). Yet to me such a view does not harmonize with the actual facts. When a leucocytosis occurs in response to the presence of organisms it is usually exclusively polymorphonuclear, although, of course, a lymphocytosis occurs sometimes. Yet what do we see in chronic myelocythaemia? A blood condition in which the proportion of the different kinds of cells varies enormously in different cases and often at different times in the same case. Again, the occurrence of eosinophil myelocytes, mast cells, and basophil myelocytes is excessively rare except in myelocythaemia, in which condition these cells are often present in enormous numbers (Dickson).

It is true that neutrophil myelocytes may be present in a number of conditions including malignant cachexia; but this is a very different state of affairs, merely indicating an exhaustion of the marrow with regard to the formation of polymorphs—temporary or permanent, as the case may be. Similarly, the condition of the blood in a well-marked case of lymphocythaemia is entirely different from any other known condition. Again, it would be reasonable to expect an initial leucocytosis of normal cells if an infection played any direct part in the process; yet no such leucocytosis has been reported. Again, intercurrent suppuration in leukaemia is characterized by the exclusive presence of polymorphs in the pus, showing that leukaemic cells are of little use in repelling the attacks of ordinary germs.

Experimental evidence is also against an infective origin. Patients suffering from malignant disease are unusually susceptible to intercurrent affections; but Schuffer injected leukaemic blood into four carcinomatous patients without any leucocytosis or other abnormality resulting. In one case there was leucopenia before and after the injection. Weil and Clerk found that intravenous injection of the blood of a leukaemic dog into another dog was fruitless. Injection into the peritoneal cavity and transplantation of leukaemic tissue under the skin were also unsuccessful.

The results of treatment are interesting in connexion with the etiology. The X-rays are often of considerable temporary benefit in chronic leukaemia. Leucolysis, a 'swinging' temperature, and gradual diminution of white cells in the blood usually occur, and for a time the blood may almost return to normal. Sooner or later application of the rays ceases to benefit, the condition relapses, and death takes place (Williams). The injection of Coley's fluid

in leukaemia is also interesting. Larrabee gave it in four cases, of which two chronic ones showed marked temporary improvement; another case showed improvement in weight and general condition only, while the fourth (acute) showed no improvement. Coley, in a recent paper, claims to have cured every variety of sarcoma except melanotic, and states that instances have been reported in which the latter tumours have vanished as the result of an intercurrent attack of erysipelas. He says that improvements in the preparation of the toxin and increased experience have enabled him to get better results than formerly. He claims to have cured eleven per cent. of his cases, although many were instances of post-operative recurrence. Both Coley's fluid and the X-rays seem to exert a more destructive effect on abnormal as opposed to normal cells, though the margin of safety is often very slight and considerable experience is necessary to get the best results. The administration of arsenic in large doses over a considerable period is often attended with good results, and probably for a similar reason. Nothing does any good in acute leukaemia. Although the number of white cells in the blood may diminish under treatment, the toxæmia produced by their destruction seems only to hasten the end.

Accordingly, the results of treatment may be summed up as follows:—X-rays, and Coley's fluid, do good in some cases by destroying some of the morbid cells and promoting fibrosis in the spleen and marrow. Some cases show no improvement, and others even go downhill owing to inability to resist the toxæmia induced by leucolysis. Experimental evidence shows that the X-rays produce leucolysis, together with sclerosis of the marrow and lymphadenoid tissues in animals (Batty Shaw). This evidence practically eliminates any infective origin of the disease. If leukaemia was merely a specialized form of leucocytosis the deliberate production of leucolysis could not help being injurious in every case. It is therefore quite unjustifiable to mention the term 'leucocytosis' in connexion with leukaemia. Michell Clarke points out that the irregular mitoses which are often found in the cells of malignant growth have not been described in leukaemia. With regard to this point I may quote Bashford and Murray, who say that 'a reducing division is neither constant nor characteristic of malignant disease, and that a true homology with the maturation processes of reproductive cells does not exist'.

Within the last eighteen months additional organisms have been suggested as the cause of leukaemia. White and Proescher describe the presence of spirochaetes in seven cases of pseudo-leukaemia, six cases of lymphosarcoma, and one of acute leukaemia. However, so little detail is given that it is impossible to say whether their discovery is of any value. The authors say that the length of these organisms varies from 20 to 120 μ , and that they are visible in a living as well as in a stained condition. Such being the alleged facts, it seems curious that no one else has noticed them. Holst claims that streptococcal infection was the cause in one of his cases. Forbes and Langmead, although finding post-mortem evidence of streptococcal infection in four cases (salivarius type), incline to the view that it merely represents a terminal condition. In point of

fact streptococcal infection is not uncommon in acute leukaemia, but there is no evidence in favour of its being the primary cause. Streptococci are of all bacteria the commonest in secondary affections, while the streptococcus is often found complicating other diseases as a terminal infection (Andrewes and Horder). In those cases of acute leukaemia associated with a decreased number of white cells in the blood before death, a streptococcus can usually be isolated. On injecting the blood from such cases into animals, a rapidly fatal septicaemia, but no leukaemia, results. Cases have once or twice been reported in which a terminal diminution of the white cells of the blood was accompanied by an apparent absence of organisms (Forbes and Langmead). Yet they were almost certainly present as a terminal infection. Compare this with those cases of septicaemia in which injection of the blood produces a rapidly fatal septicaemia in lower animals, although no organisms are to be found either on microscopical examination of, or inoculating culture media from, the original blood. If a case of acute leukaemia dies with a high proportion of white cells in the blood, organisms are seldom or never found. It is interesting to note that Coley uses the dead organisms from cases of septicaemia as well as from cases of erysipelas. He says that in some cases they give the best results.

Forbes and Langmead, while discussing the etiology of acute lymphocythaemia, quote my previous paper as bringing strong evidence in support of a primary affection of the bone marrow, but go on to say that such an origin as the marrow does not seem satisfactorily to explain either those cases in which the number of lymphocytes in the blood steadily declined from a high to a low figure or those in which there was a condition of relative lymphocythaemia at the single examination made shortly before death. The previously mentioned facts seem to me a satisfactory answer to their objection.

Finally, a brief consideration of the connexion between leukaemia and some allied conditions is necessary, bearing as it does both on the etiology and the classification of these diseases. Leukaemia is linked up with all sorts of apparently anomalous affections, viz. sarcoma, lymphosarcoma, chloroma, and possibly even pernicious anaemia. Any one making even a cursory examination of the literature bearing on these diseases would be appalled at the number of types described, the classifications proposed, and the cumbrous and variable terminology suggested. Thus Sternberg considers chloroma to be a variety of what he terms leukosarcomatosis. He defines leukosarcomatosis as a large-cell lymphatic leukaemia plus the formation of heterotopous growth which distinguishes it from acute leukaemia. He therefore divides chloroma into chloroleukosarcomatosis and chloromyelosarcomatosis, according to the presence or absence of granules. Yet he does not recognize the small-cell leukaemia with heterotopous growth as belonging to leukosarcomatosis. Could anything be more unwieldy? There would not appear to be any fundamental difference between Sternberg's leukosarcomatosis and the large-cell non-granular leukaemia. The presence of a few granulocytes does not warrant further subdivision either in acute leukaemia or chloroma.

Heterotopous growth is characteristic of all acute leukaemias; e.g. the kidneys are nearly always extensively affected. In short, the separation of certain forms under the heading of leukosarcomatosis will not hold, and the retention of the term is unwarranted. The so-called myeloma affords a ludicrous instance of unnecessary multiplicity of terms. On the strength of two cases (one reported by Sternberg, in which cytoplasmic granulation was described, the second reported by Ribbert, for which an erythroblastic nature was claimed), Lubarsch divides the condition into myelocytoma, lymphocytoma, and erythroblastoma. However, Christian, in a comparative study of eleven cases, comes to the conclusion that they are plasma-cell tumours and have nothing to do with leucoblastic and erythroblastic tissue. He says that no individual has previously studied more than three cases, that Sternberg is the only observer who has succeeded in demonstrating granules in the cells of a myeloma, that haemoglobin staining of plasma cells was common in his cases, and that it often occurred in other conditions, especially in the spleen. It would seem that Christian's conclusions are undoubtedly correct, since myeloma is always associated with the presence of Bence Jones's albumosuria, which is not present in leukaemia and allied conditions. Moreover, other observers have regarded these tumours as being composed of plasma cells.

Much confusion has resulted owing to the variety of cases for which the term 'pseudoleukaemia' has been employed. Michell Clarke suggests that if the name is used at all, it should be restricted to those cases in which there is a constant relative increase of non-granular cells in the blood—the so-called aleukaemic stage of leukaemia. Accordingly I shall refer to this condition later as the pseudo-leukaemic stage of leukaemia.

The term leukanaemia has been applied to a somewhat vague condition supposed by some to be the expression of a transition from pernicious anaemia to leukaemia. Hunter reports a case in which the blood altered during the last few weeks of life from a state of pernicious anaemia to one of acute leukaemia. He takes this as indicating a reversion to the colourless ancestors of the red corpuscles. Unfortunately no post-mortem examination was made. Drysdale describes one case and quotes eleven others. He says that although normoblasts and megaloblasts are associated with an increasing anaemia of the pernicious type, there is no evidence of haemolysis to be found after death. There is seldom definite leukaemia, although large mononuclears form a considerable though variable proportion of the cells present. Large mononuclears and granulocytes are present in the marrow, spleen, liver, and sometimes the kidneys as well, i.e. the post-mortem changes resemble those of acute leukaemia. Waterhouse has recently reported a case of acute leukaemia characterized during life by a relative increase of non-granular cells and marked secondary anaemia of the pernicious type. He diagnosed acute lymphatic leukaemia and the results of the autopsy bore out his diagnosis. Normoblasts and megaloblasts, together with a high colour index, are sometimes present in ordinary cases of acute leukaemia (McCrae). It thus appears that in the small group of cases set

apart under the heading of leukanaemia, the colourless ancestor of the red cell is chiefly or entirely affected, and that such cases gradually shade off into acute leukaemia of the ordinary type. The fact that these cases may occur in early life, that there is no evidence of haemolysis at the autopsy, and that many of the changes of acute leukaemia are present, proves the condition to be entirely different from ordinary pernicious anaemia.

It would take too long to describe the various tumours affecting lymphadenoid tissue and their relation to leukaemia. However, there seem to be all varieties between the simple lymphoma, lymphosarcoma, and ordinary sarcoma. As a rule the blood is unaffected or merely shows a slight secondary anaemia. Sometimes there is leucopenia, sometimes a slight but variable lymphocytosis. Cases of glandular lymphosarcoma have been described in which the liver and spleen were affected in the diffuse manner of leukaemia, accompanied by pseudo-leukaemic or even leukaemic blood changes. Now that the pseudo-leukaemic stage of leukaemia has become generally recognized, the publication of such cases may cease. The marrow never seems to have been thoroughly investigated in such cases, and, as Emerson says, 'the marrow from many bones should be examined before making any statement as to their involvement.' Yet possibly cases exist in which there is from the commencement an irregular or widespread involvement of the haemopoietic system.

To return to the question of nomenclature in these diseases. It seems obvious from a consideration of some of the above-mentioned types that the modern tendency towards division and subdivision has gone too far. Such terms as the following are of constant occurrence in the literature of these diseases and show that the terminology is unnecessarily redundant as well, e.g. lymphosarcomatosis, leucosarcomatosis, lymphatic leukaemia, lymphocythaemia, lymphoid leukaemia, lymphocytic leukaemia, lymphæmia, mixed-cell leukaemia, chloroleukaemia, chloromyelaemia, aleukaemic leukaemia, myeloid leukaemia, myelosarcomatosis, spleno-medullary leukaemia or leucocythaemia, myelaemia, &c. Yet textbooks go to the opposite extreme. In them some varieties are not even mentioned, while the prevailing nomenclature is quite out of date. Shaw remarks how very necessary it is for our textbooks to discard the use of the terms spleno-medullary and lymphatic leukaemia, and he is undoubtedly right. What is badly needed is a simplified terminology on rational lines. Although rare intermediate forms exist, yet certain well-marked types stand out. Why not include all the myelogenous affections in which leukaemia or pseudoleukaemia is a symptom under a general heading such as myelaemia? The word is a short one and indicates the tissue first affected, while the terms at present in use are both unwieldy and incorrect.

To return once more to the etiology. All this evidence seems to show that leukaemia (or myelaemia as I shall now call it) may be considered a mere variety of malignant disease. Yet Forbes and Langmead and also Michell Clarke object to the description of the acute form as malignant, on account of its rapidly fatal termination. Yet when we read of cases in which the kidneys

have been almost destroyed, the liver seriously damaged, and the capacity of the marrow for producing red corpuscles annihilated by what appears to be a mere purposeless overgrowth of cells—when all this apparently takes place in a few weeks, it would be wonderful if death did not rapidly occur. When the anatomical situation of the growth is taken into account, the rapidly fatal termination would seem but a poor argument against the process being a malignant one. Forbes and Langmead also take objection to my view on account of the clinical aspects of such cases, which they say closely resemble septicaemia. Sometimes there really is a terminal septicaemia, but the number of such cases is, comparatively speaking, small. Such symptoms as the 'swinging' temperature and haemorrhagic tendency, which are almost universal in the acute cases, seem to be due to a breaking down of leukaemic cells, the substances set free by their dissolution causing vascular degeneration, tendency to haemorrhages, and irregular pyrexia. (For evidence on this point see my previous paper, this Journal, 1908, i. 259.)

If we assumed this leucolysis to be due to some toxæmia, should we be justified in bringing leukaemia (myelaemia) into line with pernicious anaemia? Tallqvist has found haemolytic substances in tapeworms and malignant tumours. On injecting these into animals he slowly produced a condition of pernicious anaemia. Yet, granting pernicious anaemia to be due to the formation of haemolytic substances in the oral mucosa, intestinal wall, or elsewhere, there does not, unfortunately, seem to be any true analogy between the two conditions. Contrast the haemolysis and macrophagic activity found in the spleen and elsewhere with the redundant cellular proliferation of acute leukaemia (myelaemia). The possibility of any leucolytic poison cutting off the formation of normal leucocytes and at the same time stimulating the production of their apparently useless ancestors would appear to be very remote. It seems more reasonable to suppose that owing to some error in metabolism causing cellular irritability, the marrow, either locally or generally, gets worn out before its time, and becomes unable to restrain a ceaseless and purposeless proliferation of some of its constituent cells, thus bringing leukaemia (myelaemia) into line with malignant disease in other parts of the body.

In conclusion, it may be said that, although the leukaemias (myelaemias) are, on the whole, pretty sharply delimited from corresponding glandular affections, yet the skein may be very difficult to unravel post mortem, partly owing to the difficulties which a complete examination of the osseous system presents, and partly to the liability of these two sets of conditions extensively involving other parts of the haemopoietic system before invading the extraneous tissues of the body. Yet when we realize how small a bundle the sum total forms in the stack of disease, and think how many names have been given to variations originally regarded as distinct, but now known to be so intimately connected by intermediate types as to make classification almost superfluous, the idea that such conditions are due to some common 'cause or group of causes becomes a necessity; one becomes convinced that the variety and severity of

the affection varies only with the part of the haemopoietic apparatus affected, with the intensity of the stimulus, and with the ability of the organism to withstand it.

My best thanks are due to Dr. Michell Clarke for so kindly lending me his translation of Sternberg's paper.

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CRITICAL REVIEW

THE ESTIMATION AND QUANTITATIVE SIGNIFICANCE OF HYDROCHLORIC ACID IN THE GASTRIC CONTENTS

By W. H. WILLCOX

It was first shown by Prout (1) in 1824 that the gastric juice contained hydrochloric acid. The methods he adopted were as follows:—

(a) Some of the contents of a stomach were distilled and towards the end of the process hydrochloric acid passed over.

(b) Two equal portions of gastric contents were taken. One was evaporated to dryness and incinerated, the other was made alkaline with potash and then evaporated to dryness and incinerated. In the ash of each the chlorine was estimated by precipitation as silver chloride, and the difference in the amount of chlorine found in the two portions was due to the free hydrochloric acid and the volatile chlorides which had been driven off in the one case and not in the other after ignition. Prout found that the hydrochloric acid determined by this method corresponded closely to the total acidity of the gastric contents as found by titration with standard alkali, and he rightly concluded that the acidity of the gastric juice was due to hydrochloric acid. At the time of their publication Prout's results were severely criticized, and his conclusions were not accepted by physiologists for many years. The methods of analysis adopted by Prout were very ingenious and reliable, and soon his results were confirmed by numerous workers in different countries (Children, Braconnot, Tiedemann, Gmelin, &c.).

C. Schmidt worked for many years on the nature of the acid in the gastric juice (2), and in 1852 a classical work on digestion by Bidder and Schmidt appeared in which the results of Schmidt's experiments were fully given. Schmidt fully confirmed Prout's work, and found that the gastric juice examined by him always contained more hydrochloric acid than was sufficient to neutralize all the bases present, and that the excess of hydrochloric acid was alone sufficient to account for the entire acidity of the gastric juice. The experimental part of Schmidt's work was confirmed by other workers, e.g. Richet (3), Maly (4), and others, and the presence of hydrochloric acid in the stomach was accepted as proven, and also that in the gastric juice of healthy animals the acidity was accounted for by the hydrochloric acid present.

During the last thirty years numerous methods have been devised for detecting and estimating hydrochloric acid in the contents of the stomach, and an enormous amount of attention has been devoted to the subject.

Before reviewing the more important of these methods and tests it will be well to consider the forms in which hydrochloric acid occurs in the contents of the stomach. Hydrochloric acid may exist as—

- | | |
|-------------------------------------------------------------------------------------------------------------|-----------------------------|
| (i) Free hydrochloric acid, i.e. the acid is not combined with any base either inorganic or organic. | } Active hydrochloric acid. |
| (ii) Hydrochloric acid which is combined— | |
| (a) with proteins, | |
| (b) with other nitrogenous organic bases. | |
| (iii) Hydrochloric acid which is combined with inorganic bases to form neutral salts, e.g. sodium chloride. | |

Since the hydrochloric acid which is free (i), or which has become combined with proteins or organic bases (ii), must all have been originally secreted by the gastric glands, and represents the amount of hydrochloric acid in the gastric contents secreted by the stomach, it is convenient to use a term which will express these two varieties of hydrochloric acid. The term 'active hydrochloric acid' has been used for this purpose (5, 6, 7, 8) and means 'the free hydrochloric acid + the hydrochloric acid combined with proteins and organic bases'.

In the gastric contents free hydrochloric acid may or may not be present. It is extremely rare for hydrochloric acid combined with proteins and organic bases to be absent, and in order to obtain an estimate of the secreted hydrochloric acid in the gastric contents it is most important to know the percentage of active hydrochloric acid present.

During the past ten years it has been customary at St. Mary's Hospital, London, for chemical analyses of the stomach contents to be made as a routine part of the investigation of cases admitted for gastric symptoms. Considerably over a thousand of such analyses have been made under my direct supervision, and a review of these results emphasizes the importance of estimating not only the free hydrochloric acid, but also the hydrochloric acid combined with proteins and organic bases. In many cases free hydrochloric acid has been found to be entirely absent, yet the active hydrochloric acid, or acid secreted by the stomach, has been normal.

Harley and Goodbody in their published work (9) give a great number of analyses of hydrochloric acid in the gastric contents in various pathological conditions. Their results fully bear out the importance of estimating the total active hydrochloric acid, for in the majority of their analyses the free hydrochloric acid is very much less than the hydrochloric acid combined with proteins and organic bases, usually considerably under one-fourth, so that *the only true estimate of the hydrochloric acid secreted by the stomach is the active hydrochloric acid found in the gastric contents.* Copeman and Hake (10) have published analyses of the gastric contents from fourteen cases, and these all strongly bear out the view that the free hydrochloric acid of human gastric contents is very much less than the active hydrochloric acid.

It has been the custom in the routine analyses at St. Mary's Hospital for the

gastric contents to be tested for proteins, and usually these have been found present in considerable amount, so that a considerable part of the hydrochloric acid present must have been combined with them.

If some free hydrochloric acid be added to albumen or albumose or peptone it can be at once demonstrated that none of the tests for free hydrochloric acid are given, and this being so it follows that when, as is usually the case, proteins are present in the gastric contents, a very important portion of the hydrochloric acid will be combined with them.

The amount of active hydrochloric acid present in the gastric contents usually approximates closely to the total acidity when organic acids are present in small quantity. If organic acids are present in considerable amount, then the active hydrochloric acid will be considerably lower than the total acidity (see Analyses, Table V).

In some cases it is found that the active hydrochloric acid as determined by the modified Volhard-Luttke method (Willcox) (6, 7, and 8) is above the total acidity as determined by phenol phthalein titration with alkali. This is quite uncommon. Thus, in the last fifty test meals analysed at St. Mary's Hospital, in only two was the active hydrochloric acid higher than the total acidity, and the difference was very slight. One was from a case of chronic gastric ulcer where the total acidity was equal to 0.19 per cent. hydrochloric acid, while the active hydrochloric acid was 0.22 per cent.; the other case was one of pernicious anaemia where the total acidity equalled 0.02 per cent. hydrochloric acid, while the active hydrochloric acid was 0.04 per cent. The fact of the active hydrochloric acid being slightly higher than the total acidity can be accounted for by the hydrochloric acid being combined with some volatile organic base which forms a salt neutral to phenol phthalein.

B. Moore (11) has carefully investigated the cause of this, and suggests that the hydrochloric acid is combined with an organic base. He has found that the excess of the active hydrochloric acid over the total acidity cannot be explained by the presence of ammonium chloride, because ammonia was not present in sufficient amount to account for it. Emerson has found hexone bases in cancer of the stomach, and it is possible that the presence of these will account for the excess of the active hydrochloric acid over the total acidity in exceptional cases where this occurs (12).

When the results of the analysis of a test meal as regards hydrochloric acid have to be made use of for diagnostic purposes in cases of disease, *it is of very much greater importance that the active hydrochloric acid should be known than the amount of free hydrochloric acid.* The amount of free hydrochloric acid present in cases of disease of the stomach is a very variable quantity, depending on an unknown factor, viz. the amount of proteins present. The amount of active hydrochloric acid present is usually constant within certain limits for a particular disease, and *it is this estimation which I regard as of far the greatest importance for diagnostic purposes.*

The Detection and Estimation of free Hydrochloric Acid.

In all cases before testing gastric contents for free or active hydrochloric acid they should be filtered through ash-free filter paper and the filtrate used for purposes of analysis.

Congo Red and *Tropaeolin OO* have been often used as tests for free hydrochloric acid. They are not very delicate, and they react to organic acids if present in appreciable amount.

Dimethylamidoazobenzene in alcoholic solution has been much used as a test for hydrochloric acid (Töpfer's Test), and as an indicator where free hydrochloric acid is estimated by titration with an alkali. This test is delicate for hydrochloric acid, a pink colour being produced by a strength of 1 in 100,000 of water. The characteristic change of colour is, however, produced by organic acids. Thus lactic acid in strength as weak as 1 in 10,000 and acetic acid as weak as 1 in 2,000 both give a positive reaction. The test is, therefore, not reliable as a positive test, but is useful as a negative test in showing the absence of free hydrochloric acid. I have on several occasions found that gastric contents gave a positive reaction to the test, but other more reliable tests have shown that free hydrochloric acid is absent. In such cases considerable amounts of organic acids were present.

Gunzberg's Test. This is an extremely reliable and delicate test for free hydrochloric acid. The reagent should be freshly made up for each test, because if kept it rapidly loses its delicacy. About 4 grains of phloroglucin and 2 grains of vanillin are dissolved in 1 c.c. of absolute alcohol in an evaporating dish, about 2 c.c. of gastric contents are added, and the mixture carefully heated on the water-bath; a brilliant scarlet colour is produced by free hydrochloric acid. The reaction is so delicate that 1 part in 100,000 of hydrochloric acid can be clearly demonstrated. Organic acids do not give the test (6).

Several methods have been published for the estimation of free hydrochloric acid depending on the evaporation of the gastric contents to dryness by heating on the water-bath, it being assumed that all the free hydrochloric acid is volatilized. This is quite incorrect, and hence the methods are inaccurate. It was shown (6) that if some hydrochloric acid be mixed with a solution of dextrose or dextrin, and evaporated to dryness, and then heated for two hours on the water-bath, there is only a partial loss (about one-third) of the acid. Since carbohydrates are usually present in test meals it is obvious that free hydrochloric acid will not readily be driven off by this procedure.

Physico-chemical methods have been adopted for the determination of free hydrochloric acid in the gastric contents; these are the most accurate, but they require much care and skill in their execution and can only be done by an expert analyst.

Ham and MacLeod (13) published a method depending on the hydrolysis of cane sugar by the gastric contents, and from the result the amount of free hydrochloric acid is calculated. The method takes twenty-four hours and requires a polarimeter.

B. Moore (14) published an admirable method depending on the hydrolysis of methyl acetate by the gastric contents. This method is quicker than the preceding, and is probably the most accurate method of estimating free hydrochloric acid. It takes about eight hours to perform and requires no more elaborate apparatus than a thermostat and the usual volumetric apparatus. As Moore has very clearly and fully pointed out, the physico-chemical methods of estimating free hydrochloric acid are methods really of estimating the free hydrogen ions present in the gastric contents. The result gives an estimate of the whole of the free hydrochloric acid and a portion combined with protein.

Methods of estimating the Active Hydrochloric Acid.

The following are those generally in use at the present time:—

(1) *Leo's Method* (15).—10 c.c. of the gastric contents are titrated with $\frac{N}{10}$ alkali in the presence of calcium chloride. A similar amount of the gastric contents after previous treatment with calcium carbonate is titrated with $\frac{N}{10}$ alkali. The difference in the two results is said to give the active hydrochloric acid. The objection to the method is that organic acids are estimated unless previously removed, which is very difficult. Also the hydrochloric acid is not directly estimated, but depends on an indicator which in the presence of protein may not give a sharp end reaction.

(2) *Töpfer's Method* (16).—Consists in titrating three equal parts of gastric contents against $\frac{N}{10}$ caustic soda—

- (a) With phenol phthalein as an indicator, which gives the total acidity.
- (b) With alizarin as an indicator, the difference between (a) and (b) giving the protein.
- (c) With dimethylamidoazobenzene as an indicator, which is said to give the free hydrochloric acid present.

The objection to this method is that, as Moore has ably pointed out (17), in the presence of proteins indicators such as those used are unreliable, and the results can only be approximate, since there is not a sharp end reaction; also in (c) the results will be too high if organic acids are present in appreciable amount.

(3) *Mörner and Sjöqvist's Method* (18).—In this method a portion of the gastric contents is treated with barium carbonate till all the acids are neutralized, the mixture is evaporated to dryness and ignited, and the amount of soluble barium salts is estimated by extraction with water and filtering. The barium is estimated either by a volumetric process, or better gravimetrically by precipitation as sulphate. From the result the free hydrochloric acid and that combined with protein will be obtained.

The method is a good one, but the results are sometimes lower than those

given by the method next to be described. This is probably due to the fact that all the hydrochloric acid combined with organic bases is not estimated, and also to the difficulty of complete neutralization in slimy test meals containing much mucin.

(4) *The Modified Volhard-Luttke Method* (6, 7, 8).—This method is one in which the hydrochloric acid is directly estimated. It has been tested with solutions of hydrochloric acid of known strength in the presence of proteins and substances such as those found in gastric contents, and it has been found to give extremely accurate results. Two equal portions of gastric contents are taken; to one portion pure sodium carbonate is added in excess; both are evaporated to dryness and ignited at a low red heat so as thoroughly to char and decompose the organic matter present. The chlorides in each are then estimated by Volhard's process in the dishes in which the ignition is done, without any previous filtration. The difference in the two results gives the amount of active hydrochloric acid present. The method is very simple and quick. It is well adapted for clinical purposes. There is no risk of loss from volatilization of sodium chloride, since it is quite unnecessary to heat until the ash is white. The method has been used for several years in the pathological chemistry laboratories of St. Mary's Hospital, and it is all that can be desired as a method suitable for accurate clinical work where the results are to be made use of for purposes of diagnosis.

The Quantitative Significance of Hydrochloric Acid in the Gastric Contents.

Recent physiological research on pancreatic and gastric secretion by Bayliss and Starling (19), by Edkins (20) and others, shows how great is the importance of the presence of hydrochloric acid in the gastric contents, and suggests the necessity of the medicinal administration of hydrochloric acid in cases where the gastric secretion is insufficient. The work of Bolton (21) on the pathology of gastric ulcer shows the important relationship of an excess of hydrochloric acid in the causation of gastric ulcer. Thus if gastrotoxin is introduced into the wall of the stomach of an animal, necrosis and ulcer will result, but not if the hydrochloric acid is previously neutralized by sodium bicarbonate. Lenhartz in the valuable system of treatment of cases of gastric ulcer has made use of the fact that free hydrochloric acid can be combined in great measure in the stomach with proteins administered as food. Thus raw eggs, scraped, raw, or underdone meat, &c., with milk are given for the purpose of removing free hydrochloric acid and so alleviating the symptoms and promoting the healing of a gastric ulcer.

The amount of active hydrochloric acid present in gastric contents will throw a most important light on the nature of many obscure gastric cases provided that accurate chemical analyses are considered conjointly with the clinical symptoms. It is necessary that the test meal given should be of similar composition for comparable and reliable deductions to be made, and the time of withdrawal should be from 1 to 1½ hours after its administration. The test meal which has been used at St. Mary's Hospital consists of one pint of

very weak tea (with a little milk and sugar if desired) and a round of thin buttered toast. It is a modification of Ewald's test meal. It has been found to be appetizing to the patient and to promote effectively the secretion of hydrochloric acid. At the time of withdrawal the hydrochloric acid has probably reached its maximum percentage. There is no difficulty in obtaining the gastric contents by means of a soft tube passed into the stomach provided that sufficient tubing is outside the mouth to allow of siphon action. The siphon action can be started by withdrawal of the air from the tube by means of a male glass syringe if necessary. Other test meals are in common use, but any meal similar in composition to that of Ewald or Boas (oatmeal and water) may be given. It is advisable that the test meal should not contain meat, eggs, bouillon, &c., as the large amount of nitrogenous matter present combines with the hydrochloric acid and prevents the presence of free hydrochloric acid; it also adds to the difficulty of the analysis.

The active hydrochloric acid in a normal case with the above technique is about 0.15 per cent., between 0.1 per cent. and 0.2 per cent. It does not follow if the hydrochloric acid is normal in amount that no pathological lesion of the stomach is present. Clinical symptoms must be carefully considered also. The active hydrochloric acid may be increased (hyperchlorhydria) or diminished (hypochlorhydria). In cases presenting gastric symptoms an increase of active hydrochloric acid is commoner than a diminution.

The Causes of Hyperchlorhydria.

1. *Gastric and Duodenal Ulcer.* In the great majority of cases the active hydrochloric acid is markedly increased and free hydrochloric acid is present in excess (see Table I). It is extremely rare for the active hydrochloric acid to be below the normal. In some cases of chronic ulcer (e.g. Cases 2, 3, 5, 6, 11, 12, and 13) which have been present for years the active hydrochloric acid may not be much raised, or may only be normal in amount. Usually in gastric and duodenal ulcer the clinical symptoms are characteristic, and often a lump or thickening is felt in the pyloric region. In such cases an excessive or even normal amount of active hydrochloric acid in the gastric contents is a clear indication that gastric carcinoma is not present, and often is a direct indication for gastro-enterostomy, the subsequent prognosis being good. On several occasions I have seen cases in which hyperchlorhydria existed, showing the presence on examination of a large mass in the pyloric region. The size of the tumour had raised the suspicion of carcinoma, but in all of these cases operation or autopsy has shown that the mass was due to an ulcer with inflammatory thickening around it.

TABLE I.—*Gastric Ulcer.*

(Recent cases at St. Mary's Hospital, London.)

No. of case.	Quantity (fluid ounces).	Total acidity ¹ (per cent.).	Mucin in filtrate.	Lactic acid.	Free HCl.	Active HCl (per cent.).	Ferment activity.	Remarks.
1	1	0.22	Absent	Absent	Present	0.22	High	Diagnosis confirmed by subsequent operation (gastro-enterostomy).
2	8	0.122	"	"	"	0.122	"	
3	3	0.122	"	"	"	0.122	"	
4	4	0.24	"	"	"	0.24	"	
5	2	0.175	"	"	"	0.17	Very high	
6	8	0.189	"	"	"	0.189	"	
7	?	0.297	"	"	"	0.29	Not determined	
8	?	0.263	"	"	"	0.26	"	
9	8	0.34	"	"	"	0.34	High	
10	2	0.32	"	"	"	0.31	"	
11	5	0.18	"	"	"	0.17	"	
12	3½	0.19	"	"	"	0.16	"	
13	6	0.19	"	"	Trace	0.22	"	

Cases 2, 3, 5, 6, 11, 12, 13 were chronic ulcers with much thickening around them, the symptoms being of several years' duration.

The effect of gastro-enterostomy on the composition of the gastric contents in cases of gastric ulcer is well illustrated by Table II, where the analysis is shown before and after the operation. It is seen that free hydrochloric acid was often absent after gastro-enterostomy, whereas it was always present before the operation. The active hydrochloric acid was found reduced in every case after the operation. Bile and mucin were generally found present after the operation, and no doubt they have the effect of partly neutralizing the hydrochloric acid secreted by the stomach. This may explain the remarkable cessation of symptoms which cases of gastric ulcer present after the operation of gastro-enterostomy.

TABLE II.—*Gastric Contents (before and after Gastro-enterostomy for Gastric Ulcer).*

(Recent cases at St. Mary's Hospital, London.)

No. of case.	Total acidity (per cent.)	Mucin.	Lactic acid.	Bile.	Free HCl.	Remarks.
1. { Before operation	0.297	Absent	Absent	Absent	Present	Gastric ulcer found
{ After operation	0.116	Present	"	Present	Absent	
2. { Before operation	0.292	Absent	"	Absent	Present	" " "
{ After operation	0.14	Present	"	Present	"	
3. { Before operation	0.19	Trace	"	Trace	"	" " "
{ After operation	0.05	Present	"	Present	Absent	
4. { Before operation	0.40	Absent	"	Absent	Present	" " "
{ After operation	0.31	Present	"	Present	"	
5. { Two years after operation . .	0.13	"	"	"	Absent	" " "

¹ The total acidity was calculated in terms of HCl.

2. *Hyperchlorhydria without any Lesion of the Stomach.* It must be remembered that hyperchlorhydria may exist in the gastric contents without any clinical symptoms of its presence. Usually, however, hyperchlorhydria is associated with definite gastric symptoms; and when this is the case, probably, if the symptoms are long-continued and resist treatment, some such lesion as ulcer, erosion, dilatation, or atony of the stomach is present.

3. *Chlorosis.* An excess of active hydrochloric acid is commonly present in this condition, and the well-known gastric symptoms so often met with in cases of chlorosis are in great part due to the hyperchlorhydria present.

4. *Neurasthenia with Gastralgia.* In some of these cases an excess of active hydrochloric acid is found. More frequently, however, the active hydrochloric acid is normal in amount.

5. *Atony of the Stomach.* In young females this condition is often associated with constipation and hyperchlorhydria. In some rare cases the symptoms are so persistent as to call for gastro-enterostomy, which usually gives relief.

6. *Colitis.* Cases of colitis are frequently associated with severe gastric symptoms, and an analysis of the gastric contents in many of these cases shows a marked increase of active hydrochloric acid. In two cases recently seen the colitis was accompanied by a severe and sudden haematemesis, owing to the gastric ulceration also present, which latter was associated with hyperchlorhydria.

7. *Cholelithiasis.* This has been stated to be frequently associated with hyperchlorhydria. Kaufmann (22) and Friedenwald (23) have called attention to this. The presence of hyperchlorhydria cannot, however, be made use of as a diagnostic sign of cholelithiasis, because sometimes, as has been found in the series of cases at St. Mary's Hospital, the active hydrochloric acid was considerably below normal, yet gall-stones have been found at operation.

8. *Dietetic Indiscretions.* Heavy indigestible food, alcohol, or tobacco in excess undoubtedly may cause hyperchlorhydria.

Hypochlorhydria,

or diminution of active hydrochloric acid, may be present in many conditions; the more important of these are the following:—

1. *General Conditions of Ill-health.* Febrile conditions and general diseases, apart from the presence of disease of the stomach or cancer of any part of the body, are frequently associated with diminution of active hydrochloric acid. This has been pointed out by Moore and Morton Palmer in their published papers (11, 14, 24).

2. *Gastritis* is usually associated with definite reduction of the active hydrochloric acid. In many cases this is extremely marked, so that as regards hydrochloric acid the analytical results resemble those of gastric carcinoma. Hence great care is necessary before arriving at a diagnosis of carcinoma of the stomach, and both the clinical picture and the analytical results must be carefully weighed.

TABLE III.—*Simple Gastritis.*

(Recent cases at St. Mary's Hospital, London.)

No. of case.	Quantity (fluid ounces).	Total acidity.	Mucin.	Lactic acid.	Free HCl.	Ferment activity.
1	6	0.067	Faint trace	Absent	Absent	Very low
2	1	0.065	Present	"	"	Low
3	1	0.062	Trace	Present	"	Normal

3. *Cirrhosis of the Liver.* Usually in this condition there is a marked reduction of active hydrochloric acid, due no doubt to the associated gastritis.

4. *Pernicious Anaemia.* This condition is usually associated with a very marked reduction of the active hydrochloric acid, quite as great as that in extensive carcinoma of the stomach. Ferments are frequently entirely absent. The last three cases examined at St. Mary's Hospital illustrate this very clearly (see Table IV).

TABLE IV.—*Pernicious Anaemia.*

(Recent cases at St. Mary's Hospital, London.)

No. of case.	Quantity (fluid ounces).	Total acidity (per cent.).	Mucin in filtrate.	Lactic acid.	Free HCl.	Active HCl. (per cent.).	Ferment activity.	Remarks.
1	3	0.02	Present	Absent	Absent	0.04	Absent	Diagnosis confirmed by examination of blood and by clinical symptoms
2	3	0.10	"	"	"	0.01	"	
3	4	0.02	"	"	"	0.01	"	

5. *Achylia Gastrica.* In this condition active hydrochloric acid is almost entirely absent and the intestine appears to perform all the digestive functions. The condition may exist without giving rise to any symptoms, but usually there are definite gastric symptoms, and in some cases marked intestinal symptoms, e. g. diarrhoea with intervening periods of constipation may be present. The condition may exist apart from pernicious anaemia or gastric carcinoma.

6. *Gastric Atony with Dyspeptic Symptoms.* Some of these cases show a marked diminution of active hydrochloric acid.

7. *Cirrhosis of the Stomach.* This is a rare condition, and only a few analyses have been published. Free hydrochloric acid is usually absent, and there is a marked diminution of the active hydrochloric acid.

8. *Gastric Carcinoma.* There is no doubt that in this condition there is a most marked diminution in the active hydrochloric acid, and when the disease is at all advanced free hydrochloric acid is entirely absent (see Table V). The amount of active hydrochloric acid present depends on the site of the growth. In pyloric carcinoma the amount present is greater than when the cardiac portion of the stomach is involved. Usually, wherever the carcinoma is situated in the stomach the active hydrochloric acid is below 0.1 per cent. The deter-

mination of the amount of active hydrochloric acid present is of great value for diagnostic purposes. Thus if a lump is felt in the region of the stomach and there are definite gastric symptoms, if the active hydrochloric acid is very low the diagnosis is almost certainly that of carcinoma of the stomach. There is no doubt that in some cases of gastric carcinoma the growth develops on an old ulcer; these are the cases which are likely to show in the early stages a larger amount of active hydrochloric acid than is usually the case, and it has been

TABLE V.—*Gastric Carcinoma.*
(Recent cases at St. Mary's Hospital, London.)

No. of case.	Quantity (fluid ounces).	Total acidity (as HCl).	Mucin (in filtrate).	Lactic acid.	Free HCl.	Active HCl.	Ferment activity.	Remarks.
1	7	0.098	Present	Present	Absent	0.089	Very low	In all of these cases the diagnosis was confirmed by operation or necropsy
2	$\frac{1}{2}$	0.08	"	"	"	Not determined	"	
3	$1\frac{1}{2}$	0.00	"	"	"	0.00	"	
4	?	0.087	"	"	"	0.073	Nil	
5	1	0.00	"	"	"	0.00	"	
6	7	0.153	"	"	"	Not determined	Very low	
7	15	0.182	"	"	"	0.044	Low	
8	?	0.00	"	"	"	0.00	Nil	
9	3	0.139	"	"	"	0.03	Low	
10	?	0.15	"	"	"	0.09	Not determined	
11	?	0.09	"	"	"	0.04	"	
12	?	0.04	"	"	"	0.02	"	
13	16	0.09	"	"	"	0.01	Very low	
14	1	0.16	Absent	Trace	"	0.026	"	
15	7	0.10	"	Absent	"	0.08	"	
16	10	0.17	Present	Present	"	0.04	"	
17	12	0.27	Trace	Trace	"	0.05	"	

stated that in some cases of gastric carcinoma the hydrochloric acid has been above normal. In none of the cases at St. Mary's Hospital has the active hydrochloric acid ever been found above 0.1 per cent. The total acidity may be increased in gastric carcinoma, but not the active hydrochloric acid. The increase in the acidity is due to organic acids. I have seen cases in which the active hydrochloric acid has been found to be normal or above normal, and where after operation the lump felt was suspected to be carcinoma. In every one of these cases, where there has been an opportunity of microscopical examination after autopsy, the lump has proved to be an ulcer with inflammatory thickening around it.

9. *Carcinoma of Organs other than the Stomach.* Moore and Morton Palmer have published interesting and important papers on the gastric contents in this condition. Their analyses show that the free hydrochloric acid is reduced in cases of this kind, and in many of them there is a definite reduction of the active hydrochloric acid (11, 14, 17, 24). The reduction of the active hydrochloric acid is not sufficiently great to be of diagnostic value, as Moore freely admits, because a definite reduction of active hydrochloric acid occurs in many other conditions

than carcinoma. Copeman and Hake (10) have shown that in carcinoma of other organs than the stomach in mice there is no reduction in the active hydrochloric acid, and indeed there is a slight increase present. Moore states that carcinoma in mice is not accompanied by the cachexia which is present in this condition in man, and that the two conditions are not comparable. Copeman and Hake have made some analyses in cases of carcinoma elsewhere than in the stomach in human subjects. They find that in a considerable proportion of these cases the active hydrochloric acid is not reduced. The analyses made at St. Mary's Hospital have shown that frequently in carcinoma of other organs than the stomach there is no reduction of the active hydrochloric acid, while in carcinoma of the stomach the active hydrochloric acid has been invariably reduced. In cases of carcinoma of the transverse colon, where there has been a lump in the region of the stomach, the presence of active hydrochloric acid in normal amount has been made use of in correctly diagnosing the seat of the growth as being in the colon and not in the stomach.

Moore (17) has made some very interesting determinations of the alkalinity of the blood in cases of carcinoma in man, and has found a slight increase present. He suggests that the increase may be an important causative factor in carcinoma, since a slight increase in alkalinity may lead to the rapid and atypical growth of certain cells.

Cases in Children (25).

(i) *Congenital Hypertrophic Pyloric Stenosis.* Usually free hydrochloric acid is absent and the active hydrochloric acid is much reduced. This is probably due to the marked gastritis present, because in two early cases where gastritis was absent free hydrochloric acid was present and the active hydrochloric acid was normal in amount (see Table VI).

TABLE VI.—*Congenital Pyloric Stenosis (Children).*

(Recent cases at St. Mary's Hospital, and at the Hospital for Sick Children, Great Ormond Street, London.)

No. of case.	Quantity in cubic centimetres.	Total acidity.	Mucin.	Lactic acid.	Free HCl.	Active HCl.	Ferment activity.	Remarks. ¹
1 (a)	60	0.044	Present	Present	Absent	0.029	High	Two analyses at different times
1 (b)	42	0.050	"	"	"	—	"	
2 (a)	45	0.087	"	Absent	"	—	"	" "
2 (b)	46	0.10	"	"	"	—	Normal	
3	32	0.15	"	"	"	0.15	"	—
4	20	0.21	"	"	Present	—	High	
5 (a)	46	0.076	"	"	Absent	0.076	"	Analyses at different times
5 (b)	53	0.047	"	Trace	"	0.047	Normal	
6	?	0.07	"	Absent	"	—	"	—
<i>Cured Cases.</i>								
1	55	0.18	Trace	Absent	Absent	0.175	High	Over a year after acute symptoms
2	6	0.17	"	"	"	—	"	

¹ Numbers 1 to 6 had acute symptoms.

(ii) *Pyloric Spasm in Children without thickening of the Pylorus.* Here the active hydrochloric acid has been found to be about normal (between 0.1 and 0.2 per cent.) (see Table VII).

(iii) *Marasmus in children* is associated with absence of free hydrochloric acid and a marked reduction of active hydrochloric acid (see Table VIII).

TABLE VII.—*Pyloric Spasm (Children).*

(Recent cases at St. Mary's Hospital, and at the Hospital for Sick Children, Great Ormond Street, London.)

No. of case.	Quantity in cubic centimetres.	Total acidity.	Mucin.	Lactic acid.	Free HCl.	Ferment activity.	Remarks.
1	30	0.09	Trace	Absent	Absent	Low	Cases in Great Ormond Street Children's Hospital (clinical diagnosis).
2	28	0.11	"	"	"	Very low	
3	5	0.14	"	"	"	Rather low	
4	15	0.13	"	"	"	Normal	
5	?	0.16	"	"	"	Low	
6	?	0.18	"	"	"	Normal	

TABLE VIII.—*Marasmus (Children).*

(Recent cases at the Hospital for Sick Children, Great Ormond Street, London.)

No. of case.	Quantity.	Total acidity.	Mucin.	Lactic acid.	Free HCl.	Ferment activity.
1	?	0.09	Absent	Absent	Absent	Low
2	22 c.c.	0.03	Present	Trace	"	Nil

In conclusion, I wish to express my sincere thanks to my colleagues at St. Mary's Hospital for the numerous opportunities given me of making investigations on which much of this paper is based; also to Mr. John Webster, Demonstrator of Chemical Pathology at St. Mary's Hospital, and to Dr. Reginald Miller, Medical Registrar at St. Mary's Hospital, for valuable assistance in the work.

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THE IMPORTANCE OF OPTIC NEURITIS AND RETINAL HAEMORRHAGES IN THE DIAGNOSIS OF CHRONIC SEPTIC ENDOCARDITIS

By A. W. FALCONER

WITHIN recent years much has been written on the diagnosis of chronic septic endocarditis, but with few exceptions little attention has been paid to the importance of changes in the fundus oculi in the early diagnosis of the condition, and in the vast majority of the reports on cases of chronic septic endocarditis no mention is made of the condition of the retinae and optic disks. In the acute cases, especially those of puerperal origin, and in the more or less acute cases complicated with suppurative meningitis and cerebral abscess, panophthalmitis, embolism of the central artery of the retina, optic neuritis, and the retinitis septica of von Roth have been frequently met with, but in the literature at my command I have been able to find but few references to the occurrence of double optic neuritis, apparently a toxæmic manifestation, comparatively early in the history of the chronic form of the disease.

Within the last three years I have had an opportunity of examining some fifteen cases of chronic septic endocarditis, in five of which optic neuritis, accompanied in four by recurrent retinal haemorrhages, was present. In at least two of these the presence of optic neuritis on the first examination rendered the diagnosis of septic endocarditis probable, when it was not otherwise very obvious.

The abbreviated notes of the cases are as follows :—

Case I. Female, aged 21. Admitted to the Aberdeen Royal Infirmary, March 14, 1909, under Dr. Edmond, to whom I am indebted for permission to publish the case.

Family History. One sister died of consumption, and another was at the time in a sanatorium with phthisis. The patient had had rheumatic fever at the age of 18, which lasted for 17 weeks. Since then she had had three further attacks. For 4 or 5 months before admission the patient felt tired and unfit for work, and 2½ months before admission she went to bed as she did not feel able to be up. In addition to general weakness, patient had also been considerably troubled with pain in the small of the back and with headaches. She had also occasionally vomited and her appetite had been capricious. A few weeks before admission her urine had become 'muddy', and on examination was found to contain blood. No tubercle bacilli could be found. On admission the patient was a poorly nourished, anaemic girl. The physical signs found were slight flattening at the right apex, with diminished movement and some prolongation of expiration. No adventitious sounds. No cough or expectoration. The apex beat of the heart was in the fifth space in the nipple line. At the apex there were systolic and presystolic bruits, and a double murmur at the

base. The spleen could not be felt. The urine contained blood and albumin, blood, epithelial and granular casts. No tubercle bacilli found. Quantity about 40 ounces. Calmette's ophthalmic reaction negative. The eyes showed hypermetropia, optic neuritis, and retinal haemorrhages in each. The temperature for the first ten days was taken only night and morning, and only once showed a rise above 98.6° to 99° F. When taken four-hourly it showed a constant rise to about 100°, generally at a maximum about 4 p. m. Later the temperature became and remained markedly hectic in character. The blood on admission showed 3,400,000 red cells, 10,000 white cells, with 78 per cent. polymorphonuclears. A blood cultivation made ten days after admission showed a pure culture of staphylococcus albus, which being considered a contamination was not further examined. Repeated six weeks later a similar staphylococcus was obtained, which gave all the characteristic reactions of a suppurative staphylococcus. On May 10 the patient had severe pain in the left arm, and the left radial pulse, which before had been markedly water-hammer in type, became almost imperceptible. No oedema of arm. On April 16 she complained of pain in the tips of the fingers, and these were seen to be somewhat puffy. On the 18th there were typical raised red spots as described by Osler. On June 10 several small petechiae appeared on the chest. On July 4 sudden death with symptoms of pulmonary embolism. No autopsy permitted. On April 9 the eyes were examined by Dr. Usher, Ophthalmic Surgeon, Aberdeen Royal Infirmary, who reported as follows:— 'Ophthalmoscopic examination with pupils dilated after mydriatic—both optic disks slightly swollen, and much blurred, physiological cups filled in; no white lines along the edges of the retinal blood-vessels. In the right eye there was a small flame-shaped haemorrhage at the lower part of the fundus and a grey patch behind a retinal artery, probably an old haemorrhage. The left fundus was normal, except the optic disk. Refraction of each eye estimated at 4 D. at yellow spots. The top of the right disk was focused with a +7 D., the left disk with a +8 D. lens. May 31, 1909: Fundi again examined under same conditions, retinal vessels engorged; marked antero-posterior bending of vessels at disk margin; swelling of disks scarcely 1 mm.; in the left eye there was a small haemorrhage at the upper margin of disk and white lines along the edges of an artery which passed upwards and inwards from the disk. R. V. with correction $-\frac{5}{8}$ p.; L. V. with correction $\frac{5}{8}$. Notwithstanding the deceptive appearances, which may be present in hypermetropic eyes, there is little doubt that in addition to the few small retinal haemorrhages there was a quite well-marked double optic neuritis.'

Case II. Female, aged 29. Admitted to the Bristol Royal Infirmary, January 30, 1908, under Dr. Nixon, to whom I am indebted for permission to publish the case. The patient had rheumatic fever at the age of 6, and scarlet fever at the age of 19. For five months she had been in bed in a cottage hospital with continuous pyrexia and occasional rigors. There was no history of any skin changes. On admission the patient was poorly nourished and markedly anaemic. The spleen was palpable and there was marked clubbing of the fingers. The apex beat of the heart was situated in the fifth space half an inch inside the nipple line. There was a well-marked apical systolic bruit conducted into the axilla. The urine during her stay in hospital always contained albumin and occasional blood. During her stay in hospital she had a continuous remittent pyrexia. On admission there was well-marked optic neuritis in the right eye with a swelling of +31 D. and marked blurring of the edges of the disk. Fundus emmetropic. There were also several haemorrhages around the disk. The left fundus could not be seen owing to a dense corneal opacity, the result of a previous injury. The patient had noticed no defect in her vision. A pure culture of a streptococcus longus was obtained from the blood. The patient went home at her own desire on March 16, and her further history is not known.

Case III. Male, aged 25. Admitted to the Bristol Royal Infirmary, March 20, 1908, under Dr. Nixon, to whom I am indebted for permission to publish the case. The patient had suffered from an attack of acute rheumatism in Canada in July, 1907. In December, 1907, he suddenly developed an attack of left hemiplegia which rapidly improved. He was, however, after he had been going about again, discovered to be suffering from an intermittent pyrexia. On admission the patient was found to be well nourished, not markedly anaemic, his only complaints being loss of power and rigidity in the left arm and leg. He showed a continuous remittent temperature; the spleen was not demonstrably enlarged. There was no history of any skin manifestations. The apex beat of the heart was situated in the nipple line, and there was a loud apical systolic murmur well conducted into the axilla. The urine showed intermittently albumin, blood, and granular casts. On admission the vision in both eyes was $\frac{5}{6}$ p. There was well-marked double optic neuritis with swelling in both disks of +3 D., much blurring of the edges of the disks with antero-posterior bending, and marked engorgement, of the retinal vessels. There were also several retinal haemorrhages in both eyes, situated around the disks. Numerous fresh haemorrhages were noted during the time patient was in hospital. A pure culture of a streptococcus brevis was obtained from the blood. On April 24 the patient suffered from an embolism of the right dorsalis pedis artery. Death occurred on August 17, from uraemia. No postmortem was permitted.

Case IV. Male, aged 28. Admitted to the Bristol Royal Infirmary under Dr. Prowse on January 20, 1908, to whom I am indebted for permission to publish the case. The patient had had rheumatic fever at 16, and again at 18 years of age. Since then had been well and was at work as a labourer until admission. His only complaint was breathlessness on exertion. On admission he was well nourished and not anaemic. There was no history of any skin changes nor of any attacks of pain pointing to embolism. The apex beat of the heart was in the sixth space just outside the nipple line. There was a double murmur at the base and a systolic at the apex. No enlargement of the spleen or liver could be made out. The urine was normal. There was a remittent pyrexia. On admission there was double optic neuritis, swelling of right disk +3 D., of left +2 D., marked blurring of margins of disks with antero-posterior bendings on the vessels. Physiological cups filled in. Fundi emmetropic. There were also several retinal haemorrhages in each. The patient had noticed no defect in vision. A pure culture of a streptococcus brevis was obtained from the blood. The patient only remained ten days in hospital, and then left at his own desire as he did not like being kept in bed.

Case V. Male, aged 15. Admitted to the Bristol Royal Infirmary, December 16, 1907, under Dr. Prowse, to whom I am indebted for permission to publish the case. No proper history could be obtained, but the patient was known to have suffered from pyrexia for about nine months. He had had several attacks of severe pain over the splenic region and over the lumbar region. He had been in bed off and on for about six months previous to admission. On admission, patient was a poorly nourished boy with marked anaemia. The apex beat of the heart was in the fifth space in the nipple line. There was a well-marked mitral systolic murmur. The spleen could not be palpated, but the splenic dullness was distinctly increased. The urine contained albumin and a few granular casts. For the four days patient was in hospital before his death there was a markedly hectic temperature. On admission there was marked double optic neuritis passing into atrophy. Swelling of both disks +4 D.; fundus emmetropic. No retinal haemorrhages nor white spots could be seen. No blood cultivation was made. At the autopsy there was ulcerative endocarditis affecting the mitral valves, and numerous infarcts of the spleen and kidneys. The brain was macroscopically normal.

In all of these five cases there was definite optic neuritis, affecting both eyes in the four cases in which it was possible to examine the two eyes. In none of the cases did the patients admit of any failure in vision. In only one, Case III, was there any signs of gross brain disease. In Case III there had been some weeks before admission a sudden attack of hemiplegia, in all probability embolic in origin, from which the patient had made a very fair recovery, and was in fact again able to get about. In the absence of an autopsy it is impossible to state that there was no local cause for the optic neuritis, but there appears to be nothing to suggest it. In Case V, the only case in which an autopsy was obtained, the brain was macroscopically normal. In four of the cases there were repeated retinal haemorrhages which came and went, leaving little or no trace of their presence. The only case in which they were not noted was in Case V, and in it the fundus was only examined four days before death. In Case IV the patient's only complaint was some breathlessness on exertion, and on physical examination nothing abnormal except the physical signs of aortic and mitral regurgitation was made out. There was no obvious anaemia; the spleen was not demonstrably enlarged. There was no history pointing to embolism, and the patient, except for his breathlessness on exertion, considered himself quite well. It was only on a routine examination of the fundus oculi that the suspicion of a malignant endocarditis was awakened, which was confirmed on admission by the presence of pyrexia and the recovery of a streptococcus from the blood. In Case I the patient was admitted to the Aberdeen Royal Infirmary under a provisional diagnosis of renal tuberculosis together with an old rheumatic endocarditis. The marked family history of tuberculosis and the limited movement at the right apex appeared to point to a tuberculous lesion as the cause of the haematuria. The temperature for the first ten days under observation was taken only night and morning, and showed practically no pyrexia. It was only optic neuritis and retinal haemorrhages which, in the absence of any signs of tuberculous brain disease or advanced renal disease, appeared to point strongly to the diagnosis of malignant endocarditis.

With regard to the frequency of toxæmic optic neuritis and retinal haemorrhages in chronic septic endocarditis, it is impossible to give any figures, as it is only in a very small proportion of the recorded cases that the condition of the fundus is stated. To exclude retinal haemorrhages the fundus has to be repeatedly examined, as they come and go and leave no trace of their presence, just as do many of the skin manifestations of malignant endocarditis.

Taylor in fifty-three cases of septic endocarditis saw optic neuritis six times. In four of those cases, however, there were suppurative complications within the cranium. In two there was optic neuritis without retinal haemorrhages, in both of which at the autopsy the brain was found healthy. One occurred in a girl, aged 11, in whom the autopsy showed ulcerative endocarditis affecting the mitral valve, numerous infarcts in the kidney and spleen, and a few old haemorrhages in the brain. In this case the optic neuritis was present in the left eye on admission, and was not seen in the right eye until

one month after admission. The second case occurred in a female, aged 38, in whom at the autopsy the brain and its membranes were found quite normal. In a third case, a female, aged 21, with double optic neuritis, the condition of the brain is not mentioned in the autopsy report. In several of the other cases there were retinal haemorrhages without optic neuritis. Taylor states: 'Optic neuritis may undoubtedly be the result of meningitis when this is present, but it most certainly occurs in malignant endocarditis without cerebral complications, and I am inclined to regard it as useful in confirming a diagnosis in some cases.' Dreschfeld states that he has seen retinal haemorrhages oftener than optic neuritis in malignant endocarditis, and considers it wise to examine the fundi in all cases of endocarditis. He lays stress on the value of rigors, petechiae, and optic neuritis in the differential diagnosis between typhoid fever and malignant endocarditis. Hale White reports the case of a male, aged 19, admitted to hospital with a history of several rigors. On admission he was found to be somewhat anaemic, but did not feel ill. The only physical signs found on admission were gonorrhoea, which had been acquired a month previously, a few râles at the base of both lungs, and blurring of the right optic disk. There was no cardiac murmur. The patient died some time later, and at the autopsy was found to have ulcerative endocarditis. Ebstein reports the case of a male, aged 19, who on admission was found to have double neuroretinitis, and in whom during the next few months repeated new haemorrhages were seen in the retina. The autopsy showed ulcerative endocarditis, embolic aneurysms in the cerebral vessels with circumscribed softening, oedema of the brain, and slight internal hydrocephalus. Lenhartz states that retinal haemorrhages are pretty frequent in malignant endocarditis, and lays stress on their diagnostic value, but makes no mention of optic neuritis. Gowers states that retinal haemorrhages are frequent and the disks somewhat blurred, but does not mention definite optic neuritis. Groenouw mentions retinal haemorrhages, but not optic neuritis. Michel reports a case of malignant endocarditis with numerous ecchymoses on the conjunctiva and retina, and congestion of the optic nerve. In this case, however, miliary abscesses were found in the optic nerves after death. Romberg states that 'the embolic formations of the retina are usually sure signs of malignant endocarditis, but they are not present in more than a quarter of the cases, and apparently are to be found only in the cases running a comparatively rapid course'. Eversbusch states: 'The so-called septic changes in the retina possess a certain practical significance, and possibly depend either upon intoxication or upon non-infectious capillary embolisms. In some cases they run their course without appreciable impairment of vision, and in this respect resemble the retinal changes observed in severe or pernicious anaemia. Ophthalmoscopically they appear as numerous irregular haemorrhagic foci and yellowish-white spots, which are found in the neighbourhood of the somewhat indistinct and hazy but not swollen papilla; especially at the points of division of the veins.' Schmidt-Rimpler mentions metastatic ophthalmia and retinal haemorrhages, but not

optic neuritis. Osler saw embolic changes in the retina once in ten cases. Horder in 150 cases found retinal haemorrhages noted five times, but states that this is probably too low an estimate. Optic neuritis was not noted in any of the cases. Goh reports a case of repeated retinal haemorrhages in a chronic pneumococcal endocarditis. From an exhaustive microscopical examination of the eye, he concludes that the haemorrhages are the result of toxic changes in the vessel walls. He does not mention optic neuritis. He considers the presence of retinal haemorrhages and white spots of considerable importance in indicating a septic condition in the differential diagnosis of indefinite pyrexial conditions.

There are also a considerable number of cases reported of so-called toxic optic neuritis occurring in cases of localized septic conditions due to the organisms commonly found in septic endocarditis, which etiologically may be considered in the same category as the optic neuritis occurring in malignant endocarditis. Maddox reports a case of optic neuritis in the left eye from a focus of infection in a tooth, temporarily stopped, and from which a virulent streptococcus was obtained. Augiéras reports three cases of optic neuritis, apparently caused respectively by infection from purulent otitis, suppuration following an ingrowing toenail, and ulceration of the cervix uteri. Guichemerre and Rochon-Duvigneaud report a case of optic neuritis occurring a fortnight after an insect sting on the wrist, which produced a local abscess. Jessop reports the case of a boy, aged 17, in whom there was optic neuritis in the right eye associated with an abscess bursting into the rectum. After the evacuation of the abscess the optic neuritis receded, and the vision became normal. Marcus Gunn in the discussion on Jessop's case referred to a case seen by himself in a boy, aged 15, with a one-sided retrobulbar neuritis with marked papillitis, in whom there was a tender molar, which, when removed, was found to have an abscess at its root. The neuritis began to recede a week after the removal of the tooth, and the vision quite recovered. von Graefe describes the case of a girl, aged 8, with intense double optic neuritis with loss of the perception of light, who, within a few weeks, completely recovered her vision. The treatment consisted in the administration of mercury and 'in Eröffnung eines grossen eiternden Vesicators im Nacken'. Sourdille records a case of toxic optic neuritis in consequence of a streptococcus infection. He concludes that two methods may be concerned in the production of the optico-retinal lesions following infectious ailments: (1) the anatomical elements become impregnated with toxins circulating in the blood, and (2) the lesions are caused by microbic emboli in the central vessels of the retina. Uhthoff has collected seventy-two cases of double optic neuritis in influenza, two in gonococcal infections, and one in acute rheumatism of joints. In a later contribution he has collected three further cases of optic neuritis associated with so-called acute articular rheumatism. Königshofer describes a similar case in which the vision recovered in two weeks. Bichelonne reports the case of a male, aged 22, who a fortnight after a simple angina developed optic neuritis, and he refers to several others in

the literature. He considers that it is possible that the optic neuritis depends upon a renal inadequacy permitting of the closer interaction of circulating toxins and the optic nerve. He refers in support of his views to the experiments of Rosenberg on the injection of such substances as fluoresceine and various toxins, including a staphylococcus toxin, into the general circulation of healthy animals, and their non-appearance in the cerebro-spinal fluid until some experimental damage has been done to the kidneys. Rosenberg further showed that the introduction of a staphylococcus toxin into the subarachnoid space produced an optic neuritis, although compared with diphtheritic or typhoid toxin it had a relatively feeble effect. Neither in Bichelonne's case, however, nor in von Graefe's were there any signs of renal implication. In many of the cases, however, of optic neuritis occurring in chronic septic endocarditis there is undoubted evidence of grave renal disease, and it is possible that in some of the cases the renal changes may play a part in the production of the optic neuritis.

It is possible also that some of the many cases of optic neuritis associated with septic disease of the nose and accessory sinuses are to be included in the category of toxic optic neuritis. The majority of these, no doubt, are due to direct extension to the optic nerve and many of them have been accompanied by gross septic intracranial disease. There is, however, a small minority of cases—such, for example, as an empyema of one maxillary antrum accompanied by optic neuritis of the opposite side—in which it is by no means certain that the optic neuritis is the result of direct extension and not of toxic origin. It is true that Onodi has shown even in those cases there are possibilities of direct infection of the opposite optic nerve via the posterior ethmoid cells, but the mere demonstration of a possible pathway is no proof that the optic neuritis is one of direct infection, and not of toxæmic origin. In one of my cases of septic endocarditis secondary to sinus disease the patient was admitted after having undergone several operations on his nasal sinuses. His only symptoms for many weeks were repeated rigors, a hectic temperature, a profuse intermittent discharge from the nose, and a loud diastolic aortic murmur. The fundus was repeatedly examined, and was normal up to his death. At the autopsy there was ulcerative endocarditis affecting the aortic valves, and the whole base of the brain was softened and bathed in pus with the cranial nerves running through apparently uninjured.

Fish reports eleven cases of influenza followed by optic neuritis, in ten of which disease of the accessory nasal sinuses was demonstrated, and the eleventh in Fish's opinion was not sufficiently examined. He considers it would be more appropriate to speak of optic neuritis due to sinus disease following influenza, scarlet fever, &c. Against this view it may be urged that in many of those cases of toxic optic neuritis there are no symptoms of sinus disease, that it is by no means clear that all cases of optic neuritis accompanied by sinus disease are due to direct infection, and, lastly and most important, it is certainly inapplicable to the apparently closely related cases of optic neuritis associated with suppuration in distant parts.

With regard to the value of optic neuritis and retinal haemorrhages in the differential diagnosis of chronic septic endocarditis, their main value, I think, lies in the hint they give that the condition is more serious than may be at first sight apparent. As in the great majority of cases their presence can only be determined by a routine examination of the fundus oculi, it is, I consider, of very considerable importance to examine the fundus in all cases of chronic endocarditis, and more especially is a repeated examination desirable if there is the slightest suspicion of a failure in the general health. With present-day bacteriological and clinical methods it is, in the majority of cases, comparatively simple to confirm the diagnosis once the suspicion of the malignancy of the condition has been aroused.

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A CASE OF PARTIAL HEART-BLOCK OCCURRING DURING AN ATTACK OF ACUTE RHEUMATISM

By JOHN COWAN, JAMES W. McLEOD, AND ALBERT R. PATERSON

THE accompanying tracings were obtained from a girl, aged 17, a farm servant, who was admitted into Ward 2 of the Royal Infirmary on February 25, 1909, complaining of pains in the joints of two weeks' duration.

She had always been healthy until early in January, when she began to experience aches and pains, more or less constantly, all over her body. Two weeks before admission her knees, ankles, and hip-joints became painful, and after ten days the pain became so severe that she was forced to go to bed; she then noticed for the first time that her knees were swollen, and on the next day her hands and wrists became involved. The pain interfered with sleep, but she did not think that she was fevered.

On admission, she complained but little of pain, though the right knee and ankle were swollen. She was a well-developed, muscular girl, and lay easily on her back, breathing quite quietly, though she complained of feeling short of breath. She was slightly fevered at first, but the arthritis soon subsided, and no symptoms of any kind were afterwards manifested.

The pulse for the first few days of her residence in hospital was very irregular in rhythm and somewhat infrequent, the intervals between the beats being long and unequal; but all the ventricular contractions were palpable at the wrist, and the pulse-waves were of uniform size. Cervical tracings showed that the irregularity was due to defective conduction in the *a-v* bundle, the defect being so great that every second or third auricular stimulus failed to reach the ventricle. The ventricular rhythm was thus extremely irregular, but the auricular rhythm was much more constant, though probably also abnormal. There was no evidence of any disturbance of contractility.

The irregularity gradually lessened, and the pulse was fairly regular on March 3, though tracings still showed considerable delay in conduction, but all the auricular contractions were followed by ventricular beats. As days passed the delay became less marked, but it was only on March 26 that the *a-c* interval reached the normal duration.

A considerable number of cases of full heart-block, with post-mortem examination, have now been recorded, and in all of them some definite lesion of the *a-v* bundle has been found, but it has been suggested that similar defects may arise from 'functional' or from nervous causes. Cardarelli has produced the Stokes-Adams syndrome by pressure over the vagus nerve; G. A. Gibson and Ritchie have shown that the conductivity in some cases of heart-block may be improved by the administration of atropine; and Mackenzie has demonstrated that the administration of digitalis and the act of deglutition may occasion a partial block.

The fortunate issue of our case prevents an accurate knowledge of the state

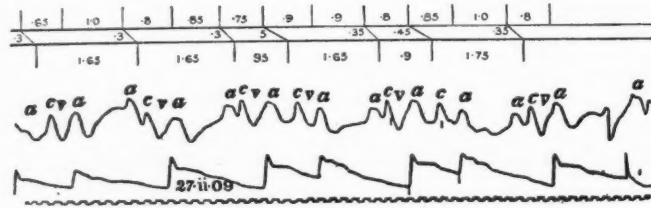


FIG. 1.

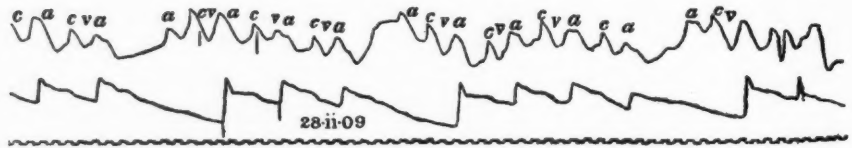


FIG. 2.

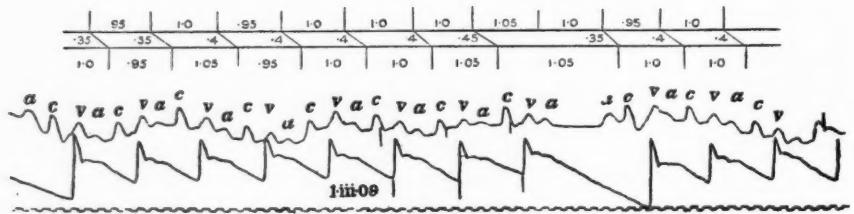


FIG. 3.

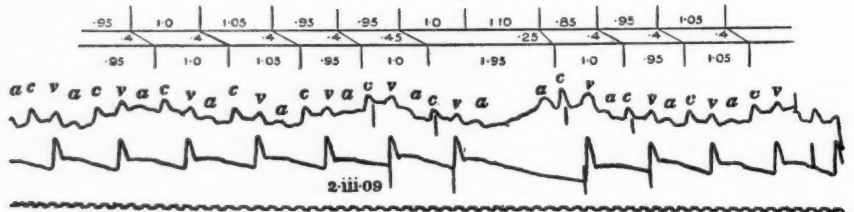


FIG. 4.



FIG. 5.

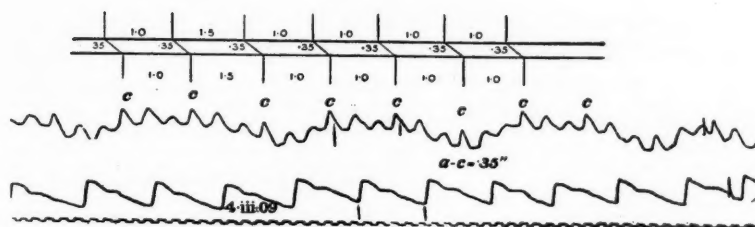


FIG. 6.

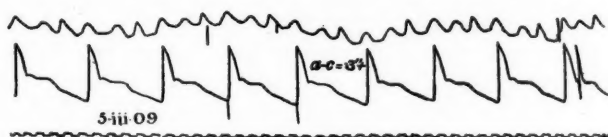


FIG. 7.

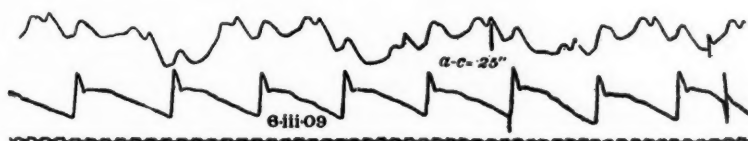


FIG. 8.

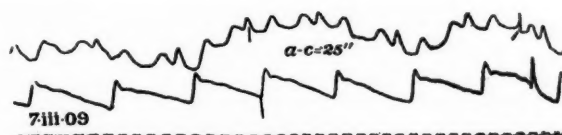


FIG. 9.

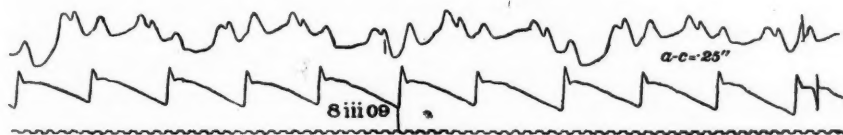


FIG. 10.

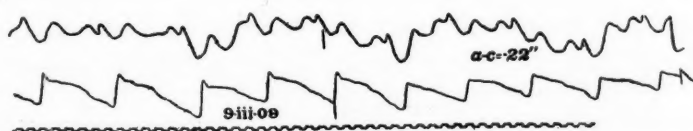


FIG. 11.

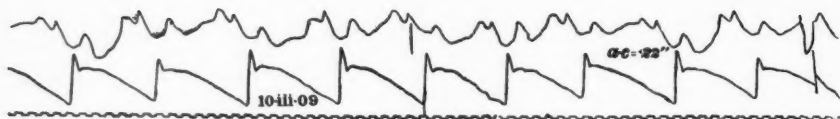


FIG. 12.

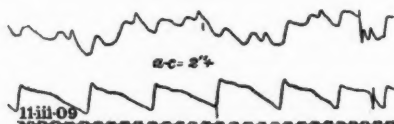


FIG. 13.

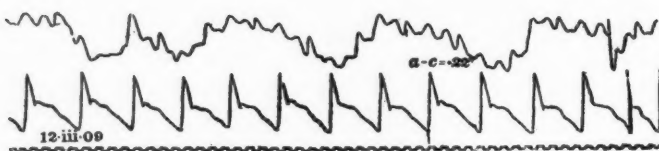


FIG. 14.

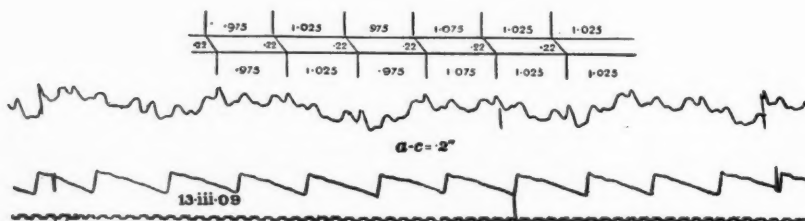


FIG. 15.



FIG. 16.

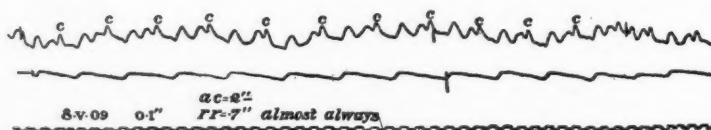


FIG. 17.

of the *a-v* bundle, but it seems to us improbable that the defective conduction was due to a nervous lesion, in view of the fact that it was not accompanied by any other evidence of nervous disturbance; while its persistence seems to negative the view that it arose from the administration of drugs before admission to hospital; and we are of the opinion that it occurred from the involvement of the bundle in some definite pathological lesion.

Inflammatory lesions in the myocardium are by no means uncommon in the acute infections (Cowan, Poynton, Coombs Carey), but they are generally microscopic in size though they may be numerous, and they are apt in consequence to escape notice unless specially looked for. The larger lesions are commonly found in septic affections, and are often only incidents in a general pyaemia; but the smaller foci are frequently present in cases of pneumonia, small-pox, enteric fever, acute rheumatism, chorea, scarlatina, &c. Microscopic sections of the muscle show here and there little collections of mononuclear cells, some of which are evidently of fixed-tissue origin, while others are obviously derived from the blood-stream. They are as a rule, but not invariably, in the immediate vicinity of an arteriole, and the muscle cells may or may not be involved in the process. If recovery occurs, little islets of fibrosis result. Arterial lesions, too, are not infrequently found in these diseases, accompanied by narrowing or occlusion of the lumen of the vessel; and Keith has shown that the central fibrous body of the heart may be damaged from this cause. It seems probable that in our case the *a-v* bundle was involved in some such lesion, with, in consequence, a temporary disturbance of its function.

A few instances of partial heart-block have already been recorded in cases similar to our own. Mackenzie has noticed it in cases of acute rheumatism (1906) and influenza (1902), and quotes (1908) cases recorded by Holst and Grosh where it occurred associated with septic affections. Wenckebach has seen it in influenza; and Jellinek and Cooper have recorded full heart-block in a case of gonococcal pyaemia, where the bundle was found to be involved in a necrotic mass. In Byrom Bramwell's case of full heart-block the *a-v* bundle was 'wellnigh obliterated' by a calcareous mass connected with a deformed mitral valve, which was almost certainly the sequel of many attacks of acute rheumatism.

Gerhardt's case is probably similar in character to that which we have described, but his tracings are unfortunately somewhat indistinct. A man, aged 25, who had had no previous illness, contracted acute rheumatism three weeks after a tonsillitis. Pericarditis and pleurisy supervened, followed during convalescence by enteric fever, which proved fatal. The pulse during the early stages of the rheumatic attack was very irregular, the ventricular beats being infrequent, probably as the result of a partial heart-block. *Post mortem*: The artery of the central fibrous body was almost occluded by endarteritis, and the *a-v* bundle was involved in an acute inflammatory process which spread but little beyond its margins.

Our case presents another point of interest. There was for long no evidence of valvular defect. The heart was apparently of normal size, and in its normal site, and the sounds, though at first somewhat short, distant, and toneless, were pure; the second pulmonic sound was not emphatic. Two months after admission (April 25), a short soft murmur was heard at the apex for the first time, and persisted.

This murmur may of course be functional in origin, but its appearance so long after the first occurrence of myocardial symptoms is (if it be a sign of organic disease) very suggestive evidence in favour of an arterial origin of the valvular infection. Poynton (1900) and Carey Coombs (1909) have urged that this is the usual pathway of infection, and have brought forward pathological data in support of their contention; and such an origin, secondary to a deep-seated myocardial lesion, would explain the insidious development of mitral lesions which is sometimes met with.

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RAT-BITE FEVER¹

By T. J. HORDER

I HAVE recently had under my care at the Great Northern Hospital a patient who was admitted on account of fever following upon a rat-bite. The man, who was a retired army sergeant, was sent to me by Dr. Hussey, of Farnham, Surrey, to whom I am indebted for a very explicit history of the onset of the disease. As I knew nothing at the time of his admission of any specific disease induced by this particular accident, and as the history prior to admission suggested an ordinary cellulitis which had since subsided, I at first thought the condition was most likely one of septicaemia due to some secondary pyogenic infection taking place during or shortly after the bite. Certain subsequent observations made on the case, however, together with Dr. Hussey's account of the early period of the illness, led me to the view that I was dealing with a state of things not readily explained by this hypothesis. The fortuitous occurrence of a very similar case about the same time, under the joint care of my colleague Dr. W. H. Willcox and Sir Almroth Wright at St. Mary's Hospital, made it probable that the disease, whatever its nature, was a definite entity. And an account which I shortly afterwards had from Dr. Bellamy, of Abbots Langley, of a very analogous case which occurred in 1907 in the practice of his partner Dr. Fisher and himself, makes this conclusion almost certain.

I will first of all append brief notes of my own case, following these by short references to the case under the care of Dr. Willcox and Sir Almroth Wright and to that under the care of Drs. Fisher and Bellamy. I wish to offer these gentlemen my thanks for their kindness in allowing me to make use of their abstracts.

Case I. George C., aged 62, admitted February 2, 1909.

History of present condition. Bitten by a rat on the right thumb on January 1, 1909. The bite was not deep and did not bleed much. Bitten on the same day by a ferret on the middle finger of the same hand; this bled more freely. The ferret-bite healed without any inflammation. The rat-bite looked 'unhealthy' for several days and the thumb was slightly swollen and painful. Eventually the bite healed completely. On January 22, three weeks after the bite, there was renewed activity in the seat of the bite itself. The thumb became much swollen and indurated on the dorsal surface, and intense lymphangitis occurred, which affected the whole arm, threatening suppuration. There was moderate fever (100°-101°) and slight malaise. In a few days things settled down and the patient seemed well. On the 29th the man again became ill, but much more so than formerly, the temperature reaching 104°; sore throat, husky

¹ A paper read before the Association of Physicians of Great Britain and Ireland, at Dublin, June 4, 1909.

[Q. J. M., Jan., 1910.]

voice, and delirium were noted. The swelling in the arm again increased and there appeared the erythema-like swellings in other parts of the body to be described later. This second attack of fever was evidently much more severe than either of the others occurring later. The local symptoms, however, were less acutely marked than during the first attack.

Past history. Abscess under the tongue in 1907. Has lived in S. Africa, Canada, Egypt, Cyprus and Malta. Denied syphilis.

Condition on admission. Looked healthy. A cicatrized dry scar on the right thumb. In centre of forearm was an elongated, red, slightly indurated and tender patch, apparently lymphatic in distribution. There was some redness and tenderness along the inner border of the biceps muscle. No tenderness or en-

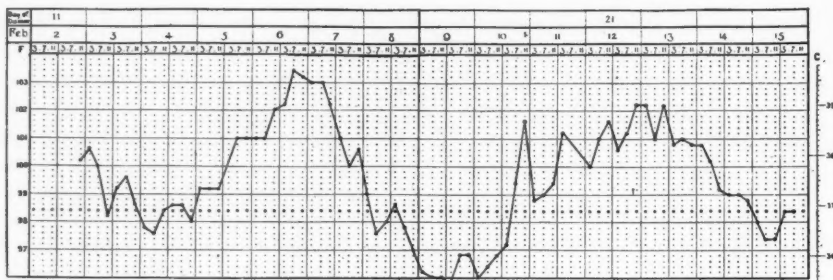


CHART I.

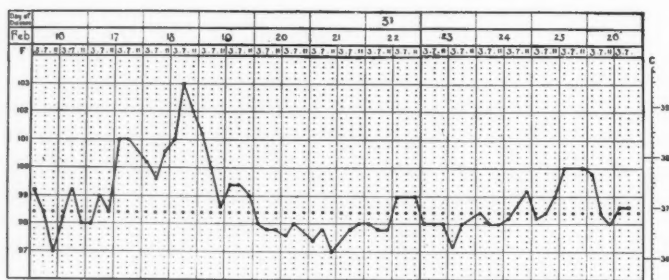


CHART I (continued). Illustrating the periodic bouts of fever between the 11th and 31st days of the disease in Case I.

largement of the axillary glands. In the skin of the forehead were three small, circular, red patches, indurated, with ill-defined margins. There was a much better defined patch over the inner canthus of the right eye, a plaque-like thickening of the skin, reddish-yellow in colour, hard to touch and distinctly tender. Two or three similar patches of red and indurated skin were seen on the legs. The tongue was furred and moist. There was no pyorrhoea. Heart and lungs appeared natural. Pulse 84. Liver and spleen not enlarged; gall-bladder not palpable. Urine: faint trace of albumin, no sugar, no casts, no blood. Temperature 100.2° (see chart for course of pyrexia). Leucocytes 18,000.

Course of the disease. In the two days following admission the temperature fell to normal, the patient having evidently come under my observation during a period of defervescence. The temperature then rose gradually, reaching 103° - 103.5°

on the fourth and fifth days, gradually falling again to normal on the seventh day, to rise again on the ninth and tenth days. Counting the rise preceding admission the patient showed five of these periodic waves of pyrexia during his twenty-five days' stay in hospital.

The erythema. A week after admission the patches of red induration became pale and soft and then disappeared. With the next bout of fever, however, two or three fresh patches appeared, best marked upon the backs of the hands. A diffuse, ill-defined, tender swelling appeared about this time in the substance of the right hamstring muscles, lasted three days, and disappeared. About the ninth day a similar lump appeared at the right side of the neck, and then passed away in two days.

The symptoms. During the pyrexial bouts the patient became ill with anorexia, mental torpor, sore throat, hoarseness, recovering rapidly as the temperature fell. There were no rigors and there was no sweating.

The leucocyte counts. These were always raised during the pyrexial periods (18,000, 19,600, 18,600), falling with the temperature (7,900, 10,000).

The following special investigations were made, with the hope of discovering the nature of the poison. As will be seen, they yielded negative results.

Blood culture. Undertaken on two occasions, during and between the febrile periods. 5 c.c. of blood from a vein in the arm yielded no growth of micro-organisms on any of the ordinary media.

Inoculation of animals. 3 c.c. of blood were introduced into the peritoneum of a guinea-pig and 2 c.c. into the veins of a rabbit. Neither animal developed any symptoms of illness.

Excision of nodules. Two of the indurated plaques in the skin of the leg were excised. One was pounded up in a small mortar and used for cultures—all proving sterile. The other was hardened and sections of it were cut. The corium showed a small round-cell infiltration in patches. Staining the sections for micro-organisms revealed nothing.

Cultivation of the urine. This proved sterile.

Blood films, stained by Leishman's and by Giemsa's methods, showed no parasites.

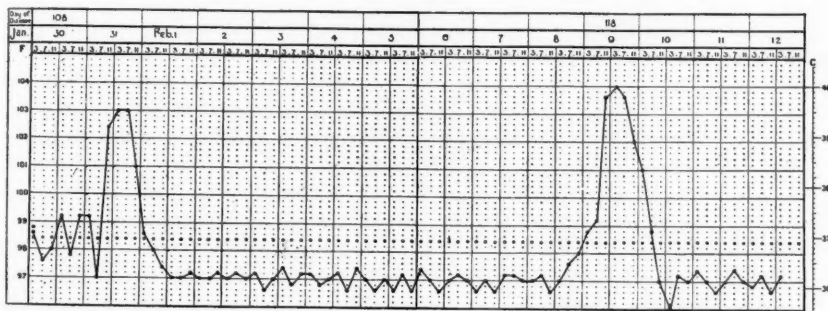


CHART II. Illustrating the periodic bouts of fever between the 108th and 118th days in Case II.

Case II. George P., aged 52 years, seaman, admitted to St. Mary's Hospital under the joint care of Sir Almroth Wright and Dr. Willcox, on January 28, 1909.

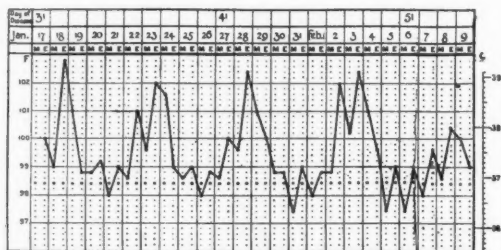
The patient was bitten by a rat on the right thumb at the end of September, 1908. The thumb became swollen and suppurated. A fortnight after the bite the thumb was poulticed, and this treatment was continued for two weeks. His doctor kept the patient in bed from October 14, and from this time there were

feverish attacks every five or six days, the attacks lasting about six hours. With these attacks there were rigors, headache, vomiting, and pains in the body. A red rash occurred at times.

The patient had had Malta fever in 1874, but no illness recently.

The man was in St. Mary's Hospital for eight weeks. About every nine days he had an attack of fever commencing with a rigor and headache. A blotchy, erythematous rash appeared on the face and body. The pyrexia lasted about twelve hours. The first three of these attacks were severe, the temperature reaching 103° - 104° . The later attacks were progressively milder; at the last the temperature reached 99.5° only. There was no enlargement of the spleen or lymph glands and no sign of suppuration in the arm or elsewhere. There was a marked leucocytosis; 19,000 on one occasion. Numerous blood cultures were made, but with negative results. Blood films were searched for malarial parasites, but none were found. The patient was treated by quinine, but Dr. Willcox is of opinion that the improvement was not to be put down to this.

CHART III.



Illustrating the periodic bouts of fever between the 31st and 51st days and between the 105th and 125th days in Case III.

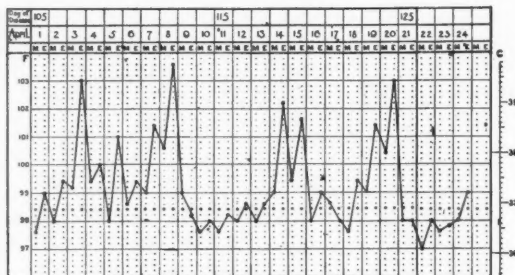


CHART IV.

Case III. John C., aged 55, gentleman farmer, was bitten by a rat on the elbow on November 9, 1907. He began to feel ill on December 7, when he came under the observation of Drs. Fisher and Bellamy. On December 16 the temperature was noted to be 105° ; again on December 23 it was high— 104° . Bouts of fever continued throughout the next four months, and it was not until early in May, 1908, that these subsided and the patient was well. The fever was markedly periodic; the rise, the fall, and the afebrile period each occupied about two days. (See Charts III and IV.)

There was no skin eruption of any kind, no pain, and no great degree of malaise. Between the febrile periods the patient felt quite fit and was able to go hunting. For some time there was a firm oedema of the bitten arm, and to this, upon the suggestion of Sir Almroth Wright, who also saw the patient, a Bier's bandage was applied. Blood examinations were negative as regards micro-organisms. Quinine, arsenic, and iron were all tried without effect.

These three cases appear to have sufficient points in common to make it probable that they are instances of a disease hitherto undescribed, at least in this country. The points to which I refer are (1) the occurrence of a rat-bite; (2) the length of the incubation period (28 days in the first and third cases, and from 21 to 28 days in the second); (3) the periodic form taken by the fever; (4) the negative results of blood culture and blood-film examinations; (5) the spontaneous recovery after prolonged duration of the disease. In two of the cases a form of erythema occurred. Rigors occurred in one case only.

To the pathogeny of rat-bite fever I am at present unable to offer any clue. The notion of malaria naturally occurs in connexion with periodic fever of this sort, but in these cases the presence of a leucocytosis, the absence of parasites in the blood films, and the absence of any enlargement of the spleen would seem to negative the suggestion. All three cases were at some stage or other treated by quinine. In my case I think it was chance that brought the defervescence and the exhibition of the drug into juxtaposition. In Dr. Willcox's case, he was of the same opinion. In Dr. Fisher's case the quinine had no effect at all upon the fever. Pyogenic infection secondary to the bite is an unlikely cause of the disease, not only because of the absence of direct evidence of this from blood culture, but also because of the long incubation period, the form of the fever, and the absence of suppuration in the original wound.

I draw attention to these cases because they probably represent a form of blood poisoning of a specific kind previously unrecognized. In cases of fever of obscure origin the influence of a rat-bite must obviously be considered. I think it probable that the *materies morbi* is of the nature of a protozoon, but in support of this opinion I can adduce nothing in the way of evidence.

REMARKS ON THE STUDY OF A CASE SHOWING A
GREATLY LENGTHENED A-C INTERVAL WITH ATTACKS
OF PARTIAL AND OF COMPLETE HEART-BLOCK, WITH
AN INVESTIGATION OF THE UNDERLYING PATHO-
LOGICAL CONDITIONS

By T. WARDROP GRIFFITH AND ALFRED E. COHN

With Plate 2

Clinical Section. (T. W. G.)

FOR the opportunity I had of making a prolonged clinical study of this case I am indebted to my colleague Dr. Barrs, who with characteristic kindness transferred the patient to my care.

The patient was a man of 29 years of age, and when he was admitted on May 21, 1908, his complaint was of dizziness and attacks of fainting. There was a history of some alcoholic excess and he had had a chancre, apparently syphilitic, eleven years previously, for which he was treated over a period of only three or four weeks. There was no history of rheumatism or chorea. He stated that he had always had good health, and although he had not taken part in athletics he had often walked all day long without any noteworthy shortness of breath. On the evening of April 19 he was walking to the public-house, when suddenly, without having any pain, he felt short of breath. He stood still for a few minutes and then went on though the dyspnoea continued. At the public-house he took two glasses of whisky, and after the second he suddenly fainted. In ten minutes he recovered and was able to walk home with his brother's assistance. It was some days before he again felt anything wrong, and then it was only a feeling of dizziness. A second fainting attack occurred at the end of a week, and from this time till the date of his admission he had frequent attacks both of dizziness and fainting, the attacks sometimes occurring twice in one day. He stated that he could usually tell when these attacks were coming on, as they were preceded by dyspnoea of about two minutes' duration, and he thought that any extra exertion tended to bring one on. He had had no cough nor oedema of the feet and did not complain of any symptoms other than those mentioned. He was in poor circumstances and for some time had not had sufficient food.

The patient was a man of moderate stature. He lay in bed with comfort in any attitude. His face was of high colour and there were some distended venules on the cheeks but no cyanosis. There was some clubbing of the ends

of the fingers and the nails were incurved. A scar was found on the penis. The physical examination indicated very clearly that he was the subject both of mitral and of aortic disease. At the base and running off from the second sound was a diastolic murmur transmitted downwards along the sternum and audible at its maximum just below the pulmonary cartilage. There was also a basal systolic bruit, but of true aortic stenosis there was no evidence in the pulse, which was sufficiently jerky to indicate a considerable though not an excessive amount of regurgitation. A diastolic thrill was felt over an area limited to the region around the apex beat. A loud, rough diastolic bruit, loudest at its beginning, was also heard with its maximum intensity at the apex. This was held to be conclusive as to the existence of mitral stenosis, but as there was also a systolic bruit at the apex which was transmitted to the mid-axillary line it was felt that the degree of stenosis could not be great. The pulmonary second sound, accentuated at the base, was also audible at the apex, and here the accent was sometimes on the diastolic bruit and sometimes on the second sound. The diastolic apical bruit was usually separated by an interval from the following first sound, but the length of this interval varied. Occasionally a contraction of the ventricle was missed out, when the diastolic bruit was heard to continue, then to increase in intensity and to last nearly or actually up to the following first sound, when it acquired something of a crescendo character. The significance of these signs and of the following note on the arterial and venous pulse made shortly after the admission of the patient by Mr. G. H. Cross, the clinical clerk, will be appreciated on a study of the tracings. 'The pulse varies greatly in frequency from 68 to 26; at irregular intervals a beat is missed, and occasionally a very feeble beat is felt. There is venous pulsation in the neck, sometimes systolic and sometimes double, systolic and diastolic.' There was manifest cardiac enlargement and the impulse was strong. There was no albuminuria.

The patient remained under my observation more or less continuously till he died on February 14, 1909. He was discharged twice, but on each occasion got rapidly worse and sought re-admission.

During his first stay in the Infirmary, and especially during the earlier part of that, he had several attacks of faintness, sometimes with loss of consciousness lasting from 30 to 60 seconds. Attacks of this kind occurred on May 26 and on June 4 and 5, and on July 10 it is noted, 'Last night patient had a fainting attack ushered in by dyspnoea; he then became cyanotic, rigid and pulseless, and was apparently unconscious for about a minute; then the pulse began to beat again and was counted at 18 per minute but soon became normal in frequency. After the attack he was very short of breath and vomited. Some dyspnoea till this morning and some expectoration of blood-stained sputum.' For considerable periods he was fairly comfortable, though his pulse varied much in frequency and presented some of the irregularities shown in the tracings. Frequently he sat up, but he would often go back to bed on account of feeling uncomfortable. One morning (July 12) he complained of discomfort with a feeling that he hardly dared to sit up in bed. The pulse was, however, quite

regular and 80 per minute. He was directed to sit up slowly in bed, and when he did so he experienced some discomfort in the head, the pulse immediately rose to 100 and the venous pulse in the neck became much more marked. He lay down and in a few minutes the pulse fell to 76.

During his second stay in the Infirmary the pulse became more jerky, cardiac dilatation increased, and the opinion was frequently expressed that the amount of aortic regurgitation was increasing.

On his third admission on December 14 there was some oedema of the legs which disappeared in a few days, occasional vomiting, much cough with slight expectoration of blood, distinct cyanosis and albuminuria. The end came suddenly on February 14, 1909. Intolerant of continuously lying in bed he had for some weeks been allowed to get up. On the date mentioned he had just gone into the lavatory when he cried out loudly for the nurse, who found him standing in the doorway with manifest dyspnoea and complaining of pain over his heart. He was wheeled to bed on a chair and died in a few minutes, no details being obtained as to the behaviour of the pulse.

The autopsy was made by myself twelve hours after death. There was much dilatation of the great veins at the root of the neck, and to this I shall return later. The heart was well covered by the lungs, which were voluminous, and there was great dilatation of all its cavities. The mitral valve was stenosed but admitted the passage of one's thumb as far as the first joint. The deformity was of the funnel-shaped rather than of the diaphragmatic variety. The aortic valve was markedly incompetent to the water test, but one's finger did not meet with any obstruction when passed up through the aperture, and there was practically no stenosis. The margins of the cusps did not meet with accuracy, and this was one cause of the regurgitation but probably not the main one. The anterior and the postero-left segments were slightly thickened and irregularly so. The postero-right or non-coronary cusp was greatly thickened, opaque and yellow. The size of the opening into the postero-right sinus of Valsalva was greater than that of the others, and the sinus itself expanded from its orifice towards its depths. There was in fact an aneurysmal dilatation of the sinus into which both the valve segment and the arterial wall entered. When one's finger was passed into this it went unduly far down, so that one could feel the rounded top of the muscular part of the interventricular septum, while towards the right the aneurysmal swelling pressed against the auriculo-ventricular junction with the result that there was some thickening of the septal flap of the tricuspid valve. The position and relations of the aneurysmal dilatation were such as strongly to suggest that there must have been pressure on the auriculo-ventricular bundle of His, and I think the increasing size of the aperture in the postero-right segment described below had tended to lessen this pressure and would account for the more regular pulse observed towards the end of life. There was a perforation of the postero-right segment of the aortic valve large enough to admit the tip of one's ring-finger, with margins smooth in one part of its circumference but elsewhere ragged as if extending and coated with adherent fibrin.

This was a second cause of regurgitation, and I associate the increasing degree of regurgitation noted during life with a gradual increase in the size of the aperture. The tricuspid aperture was about normal in size and admitted three fingers easily. The pulmonary valves were normal. There was naked-eye evidence of fatty degeneration mainly in the papillary muscles of the right ventricle. The lungs were oedematous and showed a few infarcts of various dates. There were extensive pleural adhesions on the right side. The spleen was firm, with some thickening of its capsule and old fibrous adhesions. The kidneys weighed 12 oz. and were firm, the capsules were slightly adherent, but the cortex was not diminished in amount. The testicles were normal, but the cavity of the left tunica vaginalis was obliterated. The liver extended about three inches below the costal margin, its surface showed comparatively recent perihepatitis, and on section the organ was nutmeg in appearance. The brain and its membranes were normal.

It was clear from an examination of the tracings made throughout the course of this case that the valvular lesions were associated with a great impairment of the auriculo-ventricular conductivity and with occasional attacks of heart-block. Though I was alive to the likelihood of this being due to a lesion of the bundle of His, and though I noted the history of syphilis acquired eleven years previously and very inadequately treated, I did not treat the patient for syphilitic disease, as his symptoms seemed to me to be due to failing ventricular power as in ordinary cases of valvular disease, rather than to the impairment of auriculo-ventricular conductivity. In view of the changes found on autopsy, and especially in view of the histological findings, this omission is now a matter of regret to me. The treatment by drugs consisted in the careful use of digitalis. Here again I was aware that digitalis is said to lessen auriculo-ventricular conductivity and that it may convert a partial block into a complete one. Its use in this case always seemed to be attended with temporary benefit so far as the comfort of the patient was concerned, but under its continued use missing of ventricular beats and extra systoles became more frequent and either this or a tendency to sickness led to its omission from time to time. Towards the end, when a lessened frequency of ventricular omissions seemed to imply an improved conductivity, digitalis was continued steadily but in moderation for ten days, and the pulse remained regular though frequent. I think this observation is against the final event having been due to a sudden heart-block.

It may be convenient if I show in tabular form the amount of digitalis given and the dates of its administrations. As all the charts are dated one can tell approximately how much digitalis the patient had had at the time each tracing was made.

June 16.	Tinct. Digitalis α x	every 4 hours
„ 21.	Digitalis stopped.	
Sept. 11.	Liquor Digitalis (Parke, Davis & Co.) equivalent	
	dose to α x of Tinct.	every 4 hours
„ 16.	Dose increased to equivalent of α xv of Tinct.	every 4 hours
„ 19.	Digitalis stopped.	

Sept. 26. Liquor Digitalis (= α x of Tinct.) . . .	every 4 hours
Oct. 3. Digitalis stopped.	
Dec. 18. Tinct. Digitalis α v . . .	every 4 hours
„ 20. Liquor Digitalis (= α x of Tinct.) . . .	every 4 hours
„ 23. Digitalis stopped.	
Feb. 4, 1909. Tinct. Digitalis α x . . .	every 6 hours

With the assistance of my house physicians, Mr. Arthur Fothergill and Mr. G. H. Sedgwick, I took a very large number of tracings in this case. The interpretation of many of these was difficult and there are some which, with my present knowledge, I cannot yet understand. I have been guided by a general acceptance of the views of Mackenzie. The originals of all the tracings have been carefully preserved, and with increasing knowledge and experience their meaning may be successfully revealed by myself or by others. The tracings were taken by means of Mackenzie's polygraph. With the exception of Figs. 1, 2, 15, 21, 22, and 26, which are photographs of the original tracings, all the tracings in this paper are copies of the originals. These have been made by myself on thin tracing paper with the greatest of care, and I am confident that they are within the limit of accuracy required to illustrate my remarks. By separating the jugular from the arterial or apex tracings, I have been able to put the usual form of key between them. I need hardly say I have been most careful in the insertion of the ordinates. The time marker indicates fifths of a second. The time of the carotid pulse in the jugular tracing is taken as $\frac{1}{10}$ second prior to the brachial; in many cases its exact beginning is not seen, as it is merged in a post-auricular venous wave, a wave the meaning of which I hope will become clear in the sequel. In many of the jugular tracings lines drawn parallel with the ordinates indicate the beginning of the auricular waves and the position of the carotid impacts, whether these latter are expressed as separate waves or are merged in purely venous waves. I shall discuss the tracings not in chronological order, but as they best tend to bring out the points I desire to emphasize.

The most constant feature revealed by an examination of the jugular pulse was a great lengthening of the $a-c$ interval, which was usually about $2\frac{1}{2}$ fifths of a second. For convenience, I shall refer to the length of the $a-c$ interval as being 2, $2\frac{1}{2}$, $2\frac{1}{2}$, &c., always meaning 'fifths of a second'.

Figs. 1 and 2 are tracings made on June 4; the pulse was quite regular and the patient was unusually comfortable. Both tracings show the lengthening of the $a-c$ interval. In Fig. 1 this amounts to about 2. The patient was then directed to flex and extend the elbow-joint forcibly and repeatedly. This had little effect on the pulse-rate, for it only went up from 75 to 77, but the $a-c$ interval lengthened at once to $2\frac{1}{2}$ and at the end of 20 seconds to $2\frac{3}{4}$, as shown in Fig. 2.

It is pointed out by Mackenzie that though the normal $a-c$ interval is $\frac{1}{2}$ of a second, it is usually less, it may be $\frac{1}{10}$ of a second, in hearts beating too

frequently. He also says, 'One may suspect something wrong with the *a-v* bundle when this period is $\frac{1}{3}$ of a second when the heart is beating rapidly, for the stimulus that quickens the heart rate will also quicken the rate of conduction *when the a-v bundle is intact.*' The italics are my own. I have

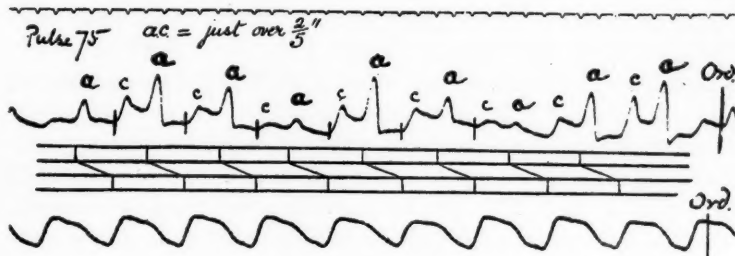


FIG. 1. June 4, 1908.

carefully measured the *a-c* interval in my earlier tracings, selecting those in which the pulse was regular, with the following results:—

	Pulse-rate	<i>a-c</i> interval
May 28	60	2 or less
" 24	65	2
June 14	70	2
" 30	71	$2\frac{1}{3}$
May 23	73	$2\frac{1}{2}$ or less
" 5	75	$2\frac{1}{3}$
" 15	77	$2\frac{1}{3}$

If these figures show anything, and they are not very definite, they show that the *a-c* interval was on the whole shorter with an infrequent pulse, or, in

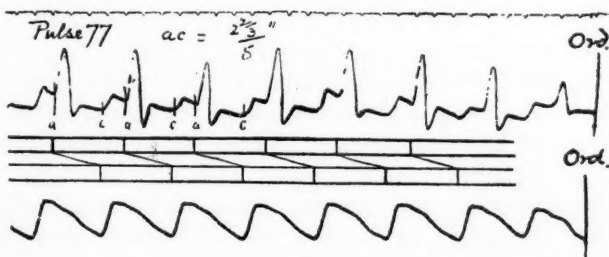


FIG. 2. June 4, 1908.

other words, the more often the bundle was called on to transmit an impulse the slower was the passage of that impulse along it. It will be interesting if further observations tend to show that in conditions of delayed as contrasted with normal conductivity an increase in the frequency of the cardiac action is associated with a lengthening and not a shortening of the *a-c* interval. The

well-known effect of the blocking of an auricular impulse in causing a shortening of the next *a-c* interval in cases of delayed conductivity, many examples of which are shown in the tracings which follow, would seem to suggest that this will prove to be the case. It is clear, however, that the difference in the length of the *a-c* interval in Figs. 1 and 2 is too great to be accounted for in this way, for the difference in the frequency of the pulse amounts only to two beats per minute. It looks as if exertion tended to impair the action of the *a-v* bundle directly, apart from any effect it may indirectly have in that way by increasing the frequency of the auricular stimuli.

The next tracing, Fig. 3, shows a phenomenon which was very common in this case, that is, the occasional blocking of an auricular stimulus leading to the omission of a ventricular contraction with a shortening of the next *a-c* interval. The *a-c* interval is here about $2\frac{1}{2}$, in the case of the first one marked it is nearly 3, and after the block it falls to just over 2. This increased rapidity of transmission is very transient, as the next impulse takes $2\frac{1}{2}$ fifths of a second

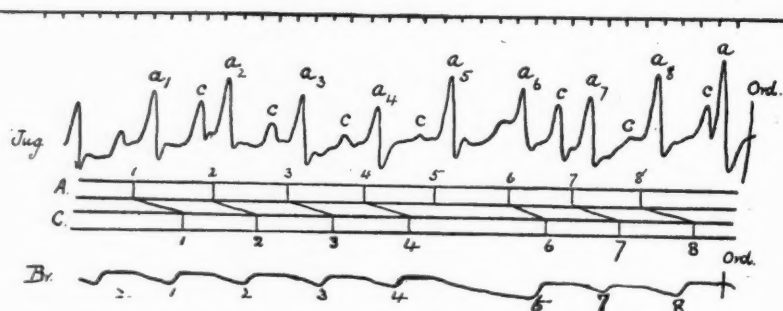


FIG. 3. May 23, 1908. Auricular pulse about 75.

to pass. It must be noted, however, that the auricular contraction, marked 7, occurred early, a condition I have frequently noticed after a block. This on the one hand may have determined the sluggish transmission of its impulse to the ventricle, the bundle being called upon to act unduly soon, and on the other hand it has caused the pulse interval following on the missed beat to be of normal and not of greater length than usual.

Before passing from these tracings I should like to point out some of the effects of this lengthening of the *a-c* interval. One is that the auricular contraction follows the ventricular contraction of the previous cycle unduly soon, and of course this is more marked in proportion to the lengthening of the *a-c* interval. It was very striking to place one's finger on the carotid and to see and feel soon or immediately after its impulse a sharp rise in the jugular vein manifestly, as the tracings show, due to auricular systole. Over the bulb of the internal jugular a distinct click was felt, and with the stethoscope one could hear at this time a sharp sound which I attributed to the closure of the valve at this

position. In making the autopsy I exposed the veins before opening the heart, and then injected water up the superior cava from the right auricle. Though the valve at the lower part of the internal jugular was not competent, each sudden pressure on the ball of the syringe was attended with a sharp click due to its partial closure or stretching. In many cases, as in Fig. 2, the auricular contraction must have occurred altogether within the period of the ventricular contraction of the former cycle, and then doubtless the auricle would fail to drive its blood into the unwilling ventricle. In other instances the auricular systole, though not following the carotid beat so soon, would occur early in the period of the ventricular diastole, and, driving the blood forcibly through the narrow mitral valve, would account for the early part of the diastolic bruit which was noted at the apex being loud and rough. When a ventricular beat was missed, as in Fig. 3, the ventriculo-diastolic bruit might or might not be continuous with the rough bruit due to the succeeding auricular systole, which, in turn, would, in respect of the shortened *a-c* interval, tend to run up to the next

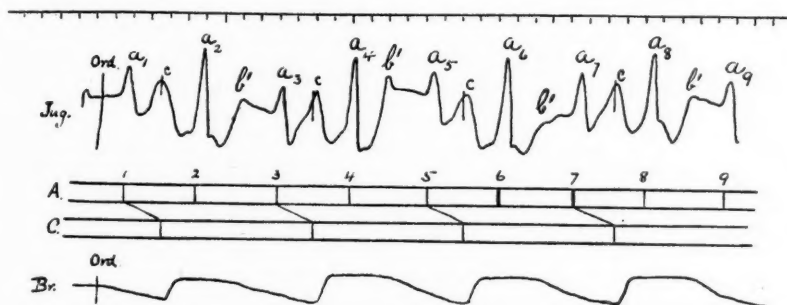


FIG. 4. June 7, 1908. For discussion of waves marked *b'* in this and subsequent tracings see end of paper.

first sound and partake more of the crescendo character of the ordinary presystolic bruit.

In Fig. 4 every second auricular stimulus is blocked and a 2:1 rhythm results. The slight prematurity of the auricular waves marked 2, 4, 6, and 8, and their pronounced character, may raise the question of their being an expression of extra systoles of *a-v* origin, but a tracing of the jugular pulse and apex beat (Fig. 5) taken a couple of minutes after shows that this is not the case and that the ventricle responds to every second auricular stimulus.¹ For premature ventricular contractions to occur at the same time as the auricular systoles marked 3 and 5 in this tracing, they would require to occur during the previous ventricular systoles, as may be seen by comparing the venous and cardiac tracings, and this is unthinkable. Nor do I think it possible for the *a-v* bundle with its deficient conductivity to transmit an impulse from

¹ Conductivity must have slightly deteriorated before the apex tracing was made, for the *a-v* interval of Fig. 5 is not shorter than the *a-c* interval of Fig. 4.

any point in its course which could reach auricle and ventricle at the time necessary for their simultaneous contraction. It could not start soon enough. I attribute the large auricular waves marked 3, 4, 6, and 8, in Fig. 4, to the previous ventricular contractions not having quite ceased, while the auricular waves marked 3, 5, and 7 are smaller, because the auricles were successfully emptying themselves into ventricles, pretty full indeed, but not contracting. I can offer no satisfactory explanation of the prematurity of the auricular beats. It is apparently of the same nature as that commented on in dealing with Fig. 3.

In Fig. 6 we find the blocking of every third auricular impulse resulting in alternately short and long pauses between successive arterial beats. The varying rapidity of conduction causes the short pause to be longer than one interauricular period and the long pause to be shorter than two such periods. Here again the long *a-c* intervals, corresponding to the auricular systoles marked 2, 5, and 8, result in the auricular systoles 3, 6, and 9 occurring before the ventricles have relaxed, and their jugular waves are in consequence very marked.

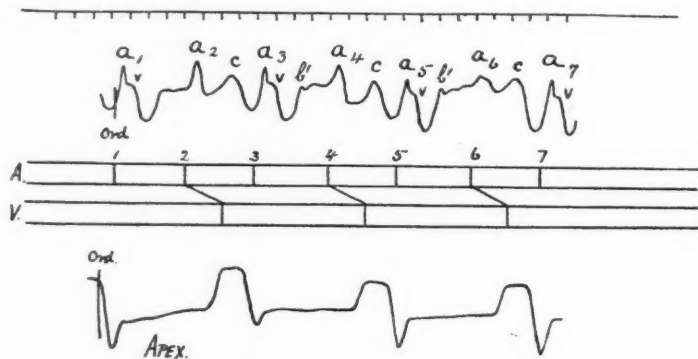


FIG. 5. June 7, 1908. For discussion of waves marked *v* in this and subsequent tracings see end of paper.

On May 26 the patient when in bed had a transient loss of consciousness, and on his recovery his pulse was found to be very infrequent. The tracings (Figs. 7 and 8) show a condition of complete heart-block. The auricles were beating at about 120 and the ventricles at 26 per minute. There was no relation between the auricular rhythm and that of the ventricles. The pulse was full and heaving and the slow emptying of the brachial artery, especially marked in the former tracing, was a striking feature. Very remarkable also were the auscultatory phenomena during this time, for between the successive seesaw bruits due to the aortic lesion one could hear a series of short, rough bruits at the apex manifestly auriculo-systolic in origin. This series merged with the seesaw bruits in various and confusing ways, as will be understood from an examination of the two tracings.

Fig. 9, and there are other tracings like it, presents difficulties in interpretation. Three explanations occur to me. Two of them are based on the

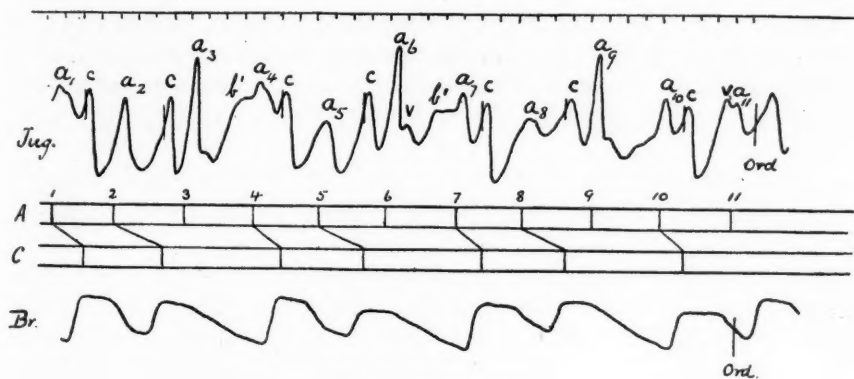


FIG. 6. June 19, 1908.

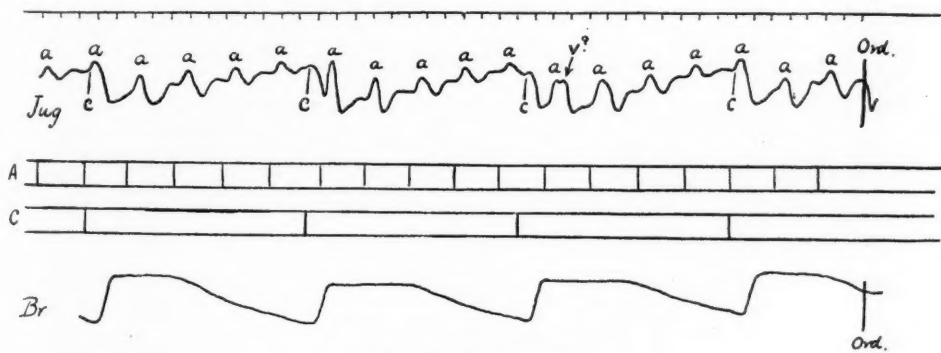


FIG. 7. May 26, 1908.

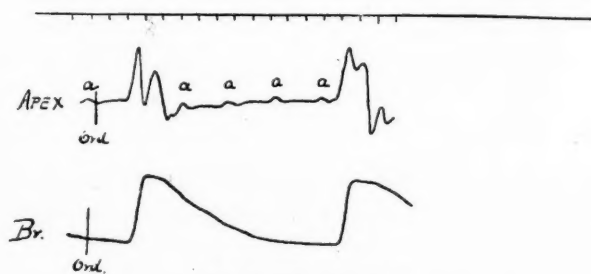


FIG. 8. May 26, 1908.

view that every third auricular stimulus is blocked, and these are indicated by the intercalated keys marked I and II. It is at variance with my experience in this case that the blocking of one stimulus could so restore conductivity as to shorten the *a-c* interval to below the normal of one-fifth of a second, and so I discard No. I. If No. II furnishes the correct explanation we must admit

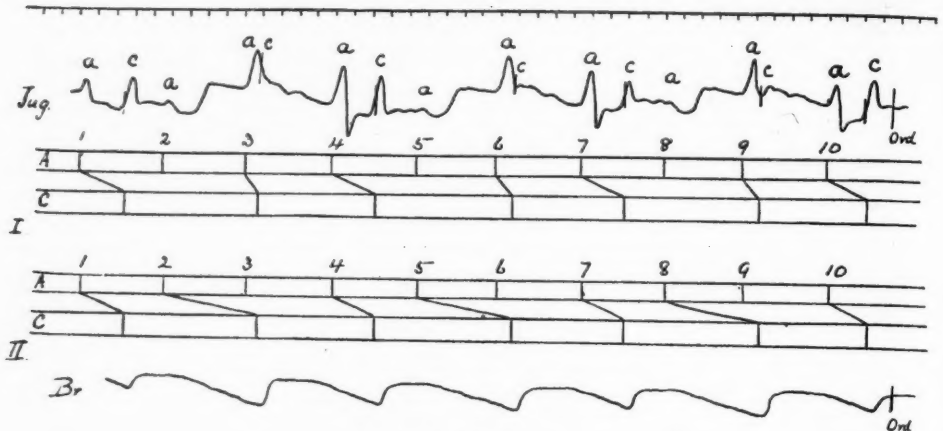


FIG. 9. May 25, 1908.

that the auricular contractions marked 3, 6 and 9 have occurred before the stimulus of the previous auricular contraction had reached the ventricle, and this is the explanation to which I incline. A third possibility is that the block was a complete one, and that we have those alternately long and short interventricular pauses which Wenkebach has described in some such cases. Against this is the

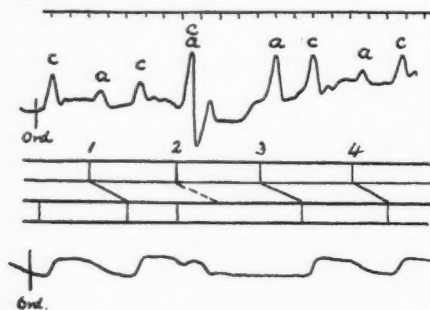


FIG. 10. May 24, 1908.

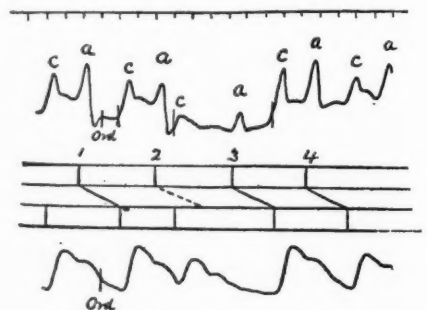


FIG. 11. June 18, 1908.

fact that the ventricles are beating at 43 per minute, while on the occasion of the undoubted heart-block just described they were, as we have seen, beating at 26.

The irregularities in the tracings discussed up to now have all been accounted for by the occasional or rhythmical blocking of auricular stimuli, but irregularity also resulted from the occurrence of extra systoles. Figs. 10 and 11 are instances

of these. In the former the carotid and auricular waves in the jugular pulse are simultaneous, and so the ventricle must have contracted a little earlier than the auricle; in the latter, though the ventricular follows the auricular contraction, it does so at so short an interval that it cannot have been due to a stimulus from the auricle. I am of opinion that both these extra systoles are of ventricular origin, and I accept the fact that the *a-c* interval following on the extra systole

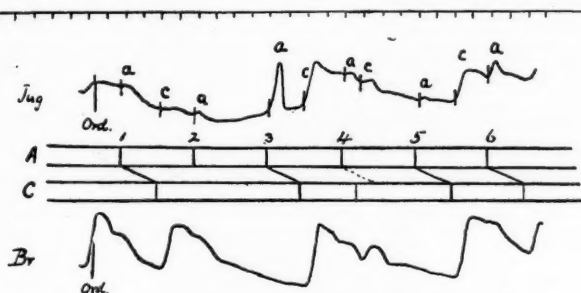


FIG. 12. May 30, 1908.

is in each case as long as that of the beat preceding it as evidence that the bundle had not had any unusually long period of rest, but that it transmitted the usual impulse from the auricle which would reach the ventricle during the refractory period of the latter resulting from the extra systole.

Figs. 12 and 13, in which unfortunately the tracings from the jugular vein are not very satisfactory, show combinations of the two main peculiarities noted.

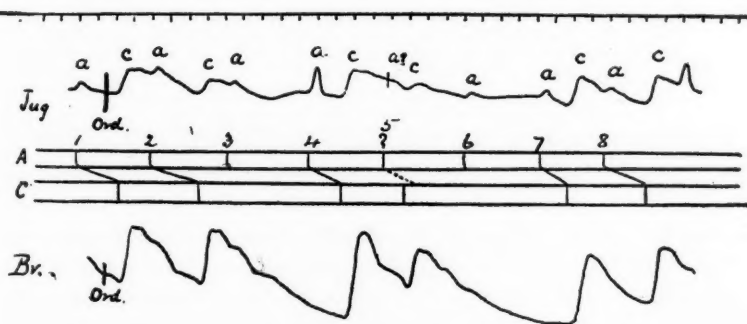


FIG. 13. May 30, 1908.

In Fig. 12 the second auricular stimulus is blocked, and so the following *a-c* interval is short. It is however only very slightly less than the first, but it must be noted that we are comparing it with an *a-c* interval itself shorter than is usual in this case. When on the other hand, as in Fig. 13, the ordinary *a-c* interval is long, the effect on the following *a-c* interval of the blocking of the third auricular stimulus is very pronounced. In both tracings the long pause is necessarily less

than the sum of the two corresponding interauricular spaces, and of course this is more marked in Fig. 13. In Fig. 12 the beat which succeeds the long pause is followed by an extra systole, I think of the ventricular variety. The 'irregular period' is of course just so much longer than its two corresponding interauricular periods as we have seen the previous long pause to be shorter than its two similar spaces. In Fig. 13 the systole which follows on the first long pause is likewise followed by an extra systole of ventricular origin, the fifth auricular stimulus finds the ventricle refractory, and the pronounced rapidity with which the seventh auricular stimulus reaches the ventricle is evidence, I think, that the sixth was blocked.

Before discussing the influence of atropine and amyl nitrite I should like to point out the effect produced on the relative time of the auricular and ventricular contractions, and therefore on the character of the jugular pulse, in such a case as this by, on the one hand, a lengthening of the *a-c* interval and, on the other, an

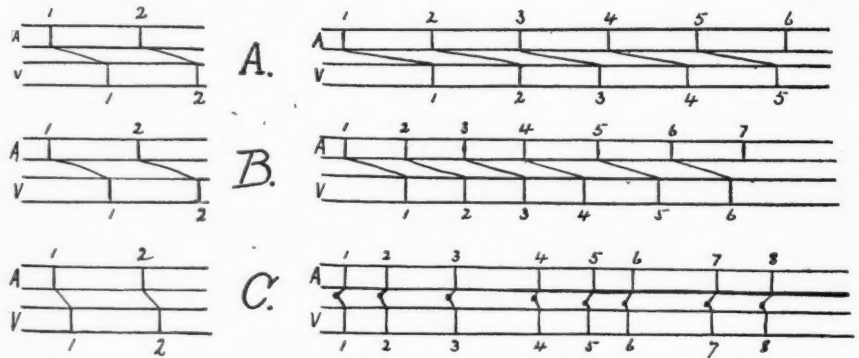


FIG. 14.

increase in the number of auricular contractions. It is clear, as shown in Fig. 14 A, that if the *a-v* interval increases so as to be equal to or nearly equal to the interauricular, the latter remaining constant, the ventricular contraction of one cycle will occur at the same time as the auricular contraction of the following cycle or very slightly before it. So also, as shown in B, if the length of the *a-v* interval remains constant the same result will ensue if there be an increase in the frequency of the auricular contractions. If there be an increase both in the length of the *a-v* interval and in the frequency of the auricular contractions the same result will be more readily obtained. The effect of this simultaneous, or almost simultaneous, contraction of the auricle and ventricle will be to produce a jugular pulse of the character described by Mackenzie in that form of rhythm to which he has provisionally given the name of 'nodal' (Fig. 14 C), in which, however, it must be noted that the auricular and ventricular systoles which occur together are those of the same and not of different cycles. It has occurred to me that the character of the venous

pulse in some of those cases of spasmodic tachycardia, in which from the absence of a separate auricular wave Mackenzie is of opinion the rhythm is nodal in character, may really be determined in this way. The nodal rhythm is, however, usually of the continuously irregular character, and it is only those rare forms in which the pulse is regular, if indeed such cases occur, that could be successfully simulated by either of the above conditions, and here the blocking

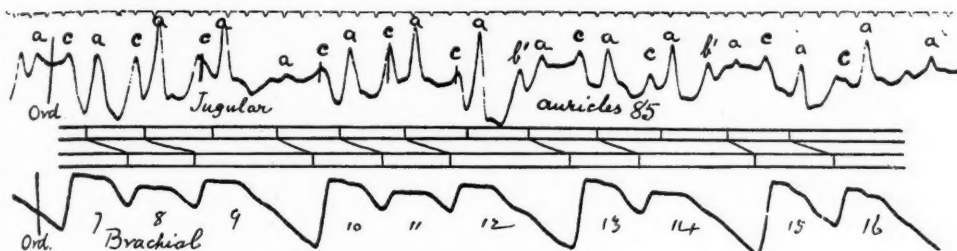


FIG. 15. June 24, 1908. Taken just before the administration of atropine at 3.30 p.m.

of a single auricular stimulus would, as will be seen in the tracings that follow, at once betray the true state of affairs.

Effects of Atropine. On June 24, three days that is to say after I had stopped his digitalis because it was causing blocking of auricular stimuli, but at a time when the patient was quite comfortable, I took the tracing shown in Fig. 15. Sometimes the fourth and sometimes the third auricular stimulus was blocked.

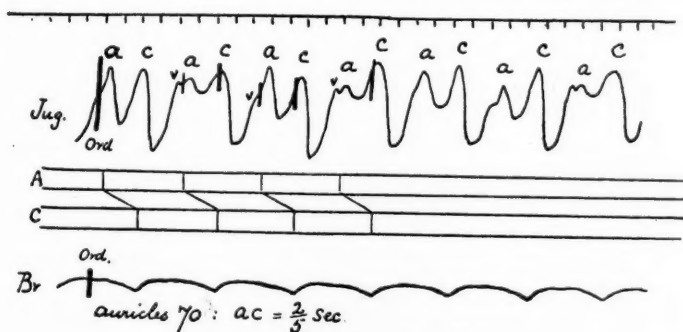


FIG. 16. June 24, 1908, 3.45 p.m.

For a few beats there was a 2:1 rhythm, but usually it was every third impulse that was blocked. The $a-c$ interval varied from a maximum of $2\frac{2}{3}$ to a minimum of $1\frac{1}{2}$, and it is to be noted that the auricular rate was 85 per minute. A hypodermic injection of atropine was then given at 3.30. This caused no discomfort, and he regarded the proceeding with indifference. At 3.45, as seen in Fig. 16, every auricular impulse got through and the $a-c$ interval was about 2. The auricles were found to be beating at 70 per minute instead of at 85, and it might

be suggested that the successful and rapid transmission of every stimulus was due to this factor. In some measure it may have been so, but it was observed that when in a few minutes this totally unexpected effect on the auricular rate had passed off, which it did steadily, and it had again risen to 86, every impulse

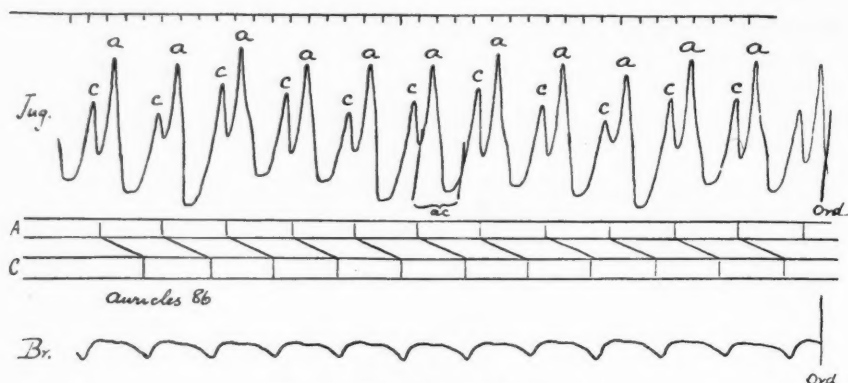


FIG. 17. June 24, 1908, 3.56 p.m.

was still passing to the ventricles, as is shown in the tracing which was taken at 3.56. Here (Fig. 17) the *a-c* interval was uniformly about $2\frac{1}{2}$. Clearly, therefore, conductivity was improved by the use of atropine. The first tracing which showed any return of the block was taken at 4.7; this is shown in Fig. 18. The auricular rate was 90, the blocking of the stimuli was irregular and infrequent,

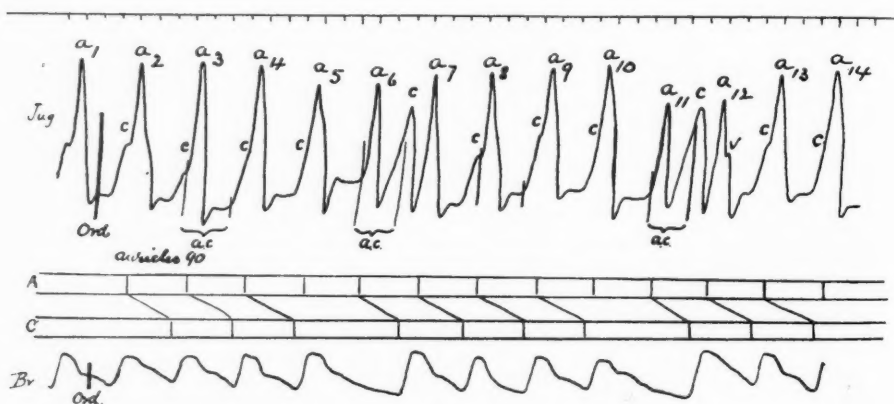


FIG. 18. June 24, 1908, 4.7 p.m.

and the *a-c* interval varied from about $2\frac{1}{2}$ before the block to about 2 after the block.

In Fig. 17, where the auricular rate is 86, the jugular tracing shows a drop between the *c* wave and the following *a* wave. In Fig. 18, where the

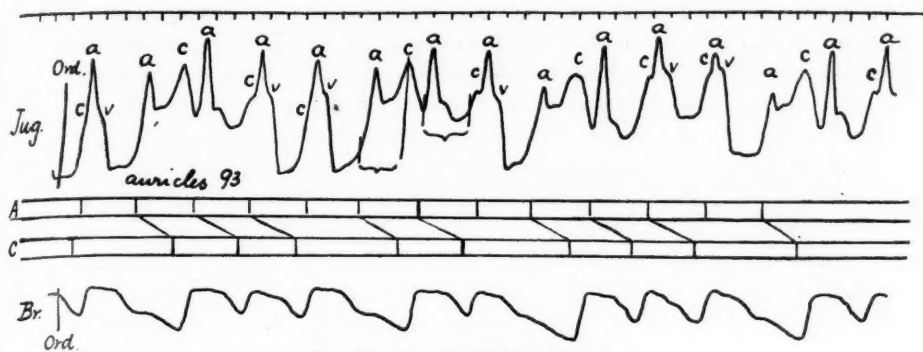


FIG. 19. June 24, 1908, 4.50 p.m.

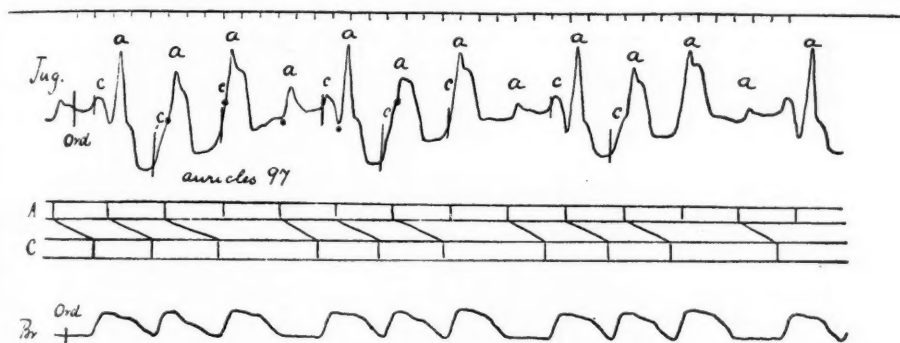


FIG. 20. June 24, 1908, about 5 p.m. The beginnings of the auricular systoles are indicated by dots.

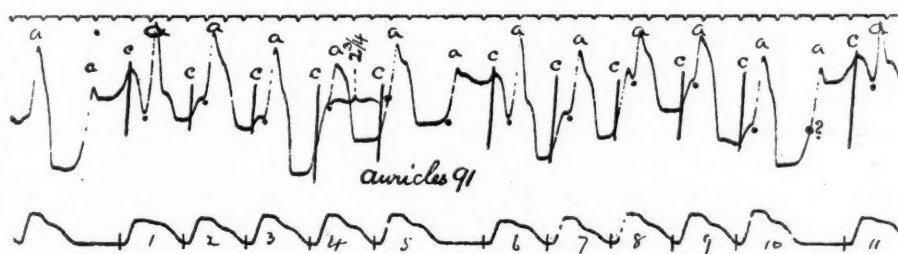


FIG. 21. June 24, 1908, about 5.5 p.m. The beginnings of the auricular systoles are indicated by dots.

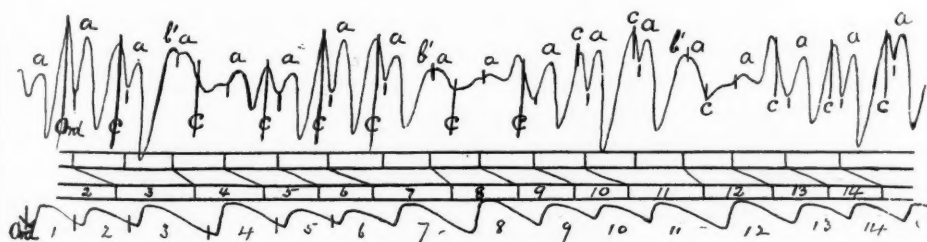


FIG. 22. December 9, 1908.

auricular rate is 90, the distinctness of this depression or even its very existence depends upon the length of the *a-c* interval. When this is short, as after the two blocked stimuli, the *c* waves occur so soon that there is a distinct chasm between them and the following *a* wave (marked 7 and 12). As the *a-c* interval lengthens again the depression becomes less marked beat by beat, so that *a* 5, *a* 10 and *a* 14 take off from the summit of the wave marked *c*, and their exact beginning cannot be seen, but must be determined as nearly as possible by comparison with those adjacent curves where the beginning of the *a* wave is distinct.

Though considerable periods of regularity continued to be noted the blocking of impulses became more frequent, occurring sometimes irregularly and sometimes rhythmically. The tracings shown in Figs. 19, 20, and 21 illustrate this and require no explanation after what has preceded. The last of these tracings was taken about 5.5; in it the auricular rate was 91, and here the greatest length of *a-c* interval is noticed, for it amounts to very nearly 3 just before the blocked stimuli.

I here introduce a tracing taken on December 9 (Fig. 22), which shows every fifth auricular stimulus blocked. Thus I have shown in this case, in addition to the extremes of an occasional block and complete heart-block, instances of the non-transmission of every second, third, fourth, fifth, and sixth auricular stimulus.

In Fig. 22 the blocking of every fifth stimulus, with the consequent variation in the *a-c* interval, leads to an alternation of two long and two short pulse spaces. The two short spaces are of equal length; of the two long spaces the earlier of the two is the longer.

Effects of amyl nitrite. On July 5, at a time when the heart had presented very little irregularity for some time, I tried the effect of getting the patient to take a few whiffs of amyl nitrite, a proceeding which did not cause him any discomfort. Fig. 23 shows the condition just before inhalation. The immediate effect of inhalation was to increase the auricular systoles from 75 per minute to 115 (Fig. 24). Conductivity was clearly improved, for although a great many more stimuli had to pass in a given time, the *a-c* intervals shortened from $2\frac{1}{2}$ to $2\frac{1}{3}$. Fig. 25 is a continuation of the same tracing, the length of time occupied by the missing beats 6 to 17 inclusive being about 6 seconds. In this tracing we find the auricular rate has fallen to 107. In the portion of the tracing not figured there was no blocking of impulses, the *a-c* intervals lengthened, and that which leads to the twentieth ventricular systole is seen to be $2\frac{1}{3}$. The favourable effect of amyl nitrite on conductivity appeared therefore to pass off sooner than its effect on the frequency of the auricular beats, or it may be that the favourable influence was more than neutralized by the frequent calls on that function. The tracing then shows the blocking of an auricular impulse with a marked recovery of conductivity lasting for some beats, for the *a-c* interval does not again lengthen to $2\frac{1}{2}$ till we reach the twenty-seventh ventricular systole.

In Fig. 24 the interauricular interval has shortened to nearly that of the *a-c* interval, and the auricular and ventricular systoles of different cycles are almost synchronous. In Fig. 25 the lengthening of the *a-c*

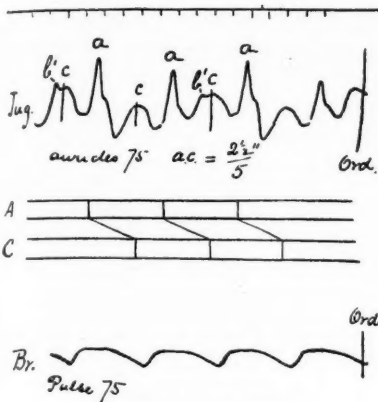


FIG. 23. July 5, 1908.

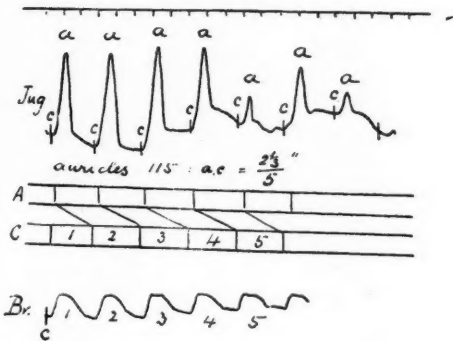


FIG. 24. July 5, 1908. Effect of amyl nitrite.

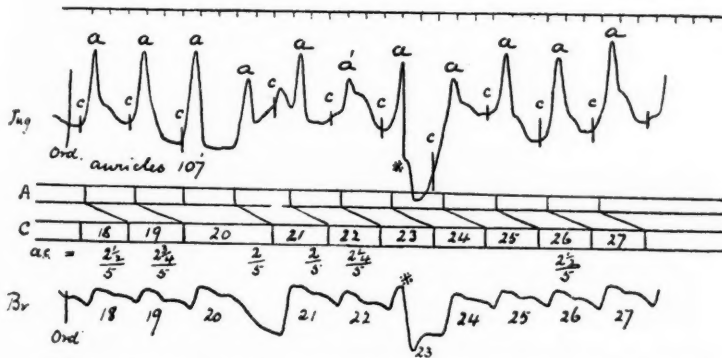


FIG. 25. July 5, 1908. Effect of amyl nitrite. The jugular and arterial levers collided at the points on the tracings marked by asterisks.

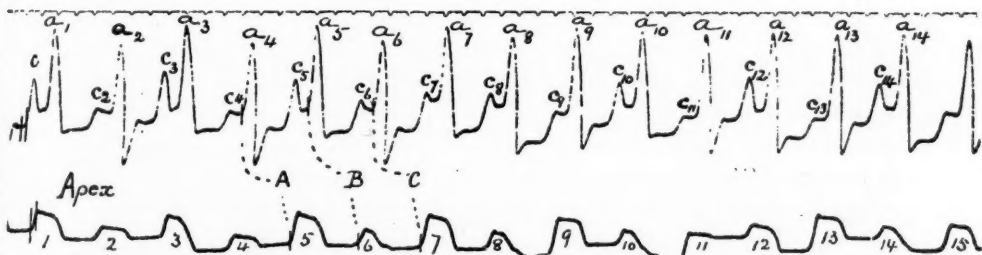


FIG. 26. June 18, 1908. Alternans action of ventricles, leading to a condition simulating an alternans action of auricles.

interval has caused this to be more marked in spite of the lessened frequency of auricular action. The more rapid transmission of the impulse following on the block separates the carotid from the following auricular wave in the jugular pulse.

Certain additional peculiarities in the tracings. On a few occasions the pulse tracings showed evidence of a slight condition of true 'pulsus alternans', that is to say with the time between the beginning of the larger beat and that of the smaller at least as long as the interval between the beginning of the small beat and that of the larger. When this was the case the auricular beats were also alternately large and small. The alternans character of the ventricular beats is well seen in the apex tracing of Fig. 26, and in the jugular tracing the auricular beats are, with the exception of No. 7, alternately large and small.

From the dotted lines leading from the letters, *A*, *B*, and *C* it can be seen that the interauricular intervals are equal though the interventricular are not. It may also be seen that the larger auricular wave is produced by that contraction of the auricle which provides the stimulus for the weaker ventricular systole, and vice versa. For example, *a* 5 gives rise to *v* 6 and *a* 6 to *v* 7. But even if we found that it was the large auricular wave which was followed by the stronger ventricular systole we could not attribute the vigour of the latter to a presumably stronger stimulus from the auricle, for of course, provided a stimulus is strong enough to cause ventricular contraction at all, it is immaterial how strong it may be. The explanation of the alternately large and small auricular waves is, I think, as follows. The primary condition is the alternans action of the ventricles. When the systoles are strong they last long enough to prevent the quickly following auricular contraction from driving the blood freely or at all into the ventricle and so a large wave is seen in the jugulars. When the ventricular systoles are weak they do not last so long, and the auricle can drive its blood in larger amount into the ventricle and consequently the jugular wave will be smaller. It is of course only when the *a-c* interval is unduly long, as it was in this case, that alternately large and small auricular waves could be determined in this way by an alternans ventricular action.

Two peculiarities in the tracings of this case remain for comment. One of these concerns the position of the ventricular wave. Now this wave to which as yet I have made no reference begins to rise during the latter part of the ventricular systole and falls just after its termination on the opening of the tricuspid valve. It is true that the duration of the ventricular systole varies in the same individual and that the exact moment of the opening of the tricuspid valve will also be influenced by the varying amount of pressure which has developed in the right auricle, but these two factors do not cause much variation in the position of the wave in question. Now we have seen that in consequence of the lengthening of the *a-v* interval in this case, the ventricular systole is followed after an unusually short space of time by the auricular systole of the next cycle. The result of this is that the ventricular wave of one systole may just precede the following auricular wave (as may indeed happen in

a frequently beating heart with a *normal* *a-v* interval), or it may blend with it, making it difficult or impossible to determine the exact beginning of the auricular wave, or—and this is the most striking phenomenon—it may actually come after it. A glance at the accompanying diagrams in Fig. 27 will make this plain. In many of the preceding tracings in which I have marked some of the *v* waves these varying relations are seen. Thus in Fig. 6, in consequence of the short *a-c* interval following on the tenth auricular systole the *v* wave has had time to culminate and begin to fall before the appearance of the eleventh auricular systole. The fifth auricular stimulus, on the other hand, is transmitted so slowly to the ventricle that there has been time for the following auricular systole to show itself before the appearance of the ventricular wave. When the *a-c* interval is intermediate in length between these two

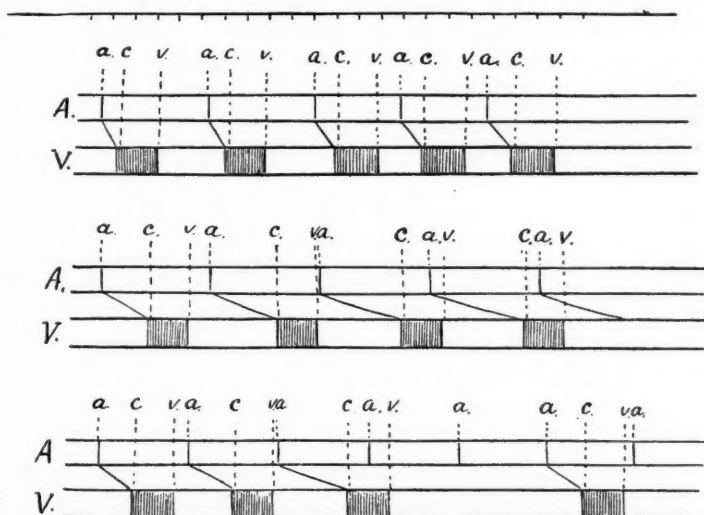


FIG. 27. The small letters show the events in the jugular pulse. The summit of the ventricular wave is marked *v*, the shaded areas indicate the duration of the ventricular systole. In the first chart, the *a-v* interval being normal, an increase in the pulse-rate from 60 to 75 causes *v* to approach the following *a* wave. In the second, a progressive lengthening of the *a-v* interval causes the *v* wave closely to approach, to blend with, or actually to follow the *a* wave of the next cycle. In the third, the same result is shown to occur without so great a lengthening of the *a-v* interval, when the heart is beating more frequently. The blocking of a stimulus is seen to result in the restoration of the normal sequence.

extremes, the *v* wave may appear merely as a hump on the ascending or descending limb of the *a* wave, or there is a more or less complete blending of the two waves, and many of the waves I have marked *a* have a *v* element in them.

The second peculiarity concerns the presence of post-auricular waves, which I think find their explanation from a consideration of the diastolic wave described by Hirschfelder and A. G. Gibson of Oxford, with which they are in many instances identical and in others closely allied. Gibson describes this

wave as occurring after the fall of the ventricular wave, and he attributes it (correctly I think) to the rush of blood from the auricle into the ventricle, on the opening of the tricuspid, temporarily closing the valves again. I quite agree with him that the wave is a common one. In Fig. 28, *D* is a tracing of my own jugular pulse and *B* and *C* show good examples of the wave from a healthy woman. (Following Gibson I have marked the wave *b*.) When *B* was taken the head was lower and the wave is more marked. In *C* the first *b* wave is ill marked and may be regarded merely as a stasis wave, between which and the pronounced variety there is every transition.

Now in a great many of the tracings I have marked a wave *b'*, and this I consider to be in many cases essentially the same as the wave just discussed, and due to the temporary closure of the tricuspid valves consequent on the rush

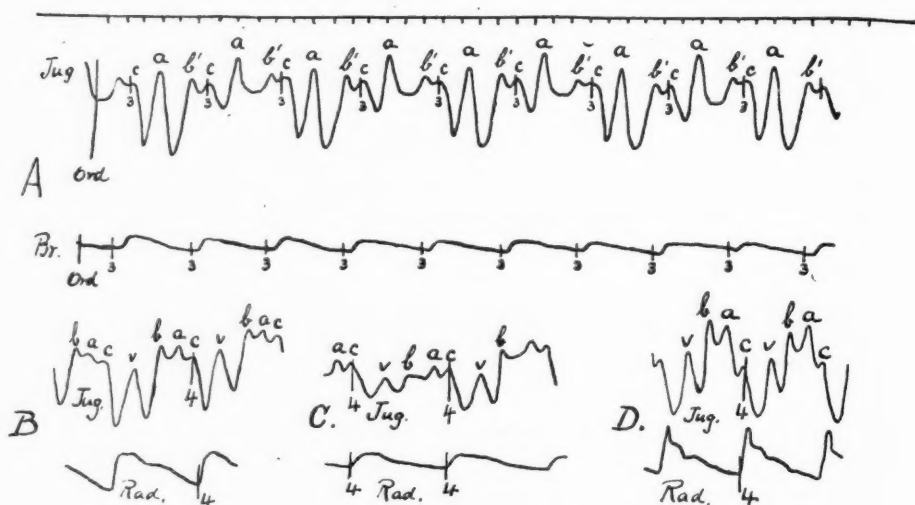


FIG. 28. (For description see text.)

of blood into the ventricles, with, it may be, some incompetence of the valve. That this rush is contributed to sometimes by the contraction of the auricle, which as we have seen usually occurs during the ventricular wave, will be obvious. The wave in my tracings is always therefore post-auricular and in many cases it obscures the beginning of the *c* wave as already mentioned, or is so large as to drown it. In many instances where an auricular contraction is not followed by a ventricular systole in consequence of a blocking of the stimulus, this post-auricular wave appears all the same and may be well marked (as in Figs. 4, 15, and others). The small post-auricular waves seen in Fig. 7 are probably of the same nature. Its obscuring of the *c* wave is seen in a great many of the tracings.

In Fig. 28 the tracing *A* was taken from my patient on Sept. 11. If this

tracing alone were put before one for interpretation it would be natural to regard the wave marked *b'* as being really the *a* wave, and to regard that which is marked *a* as purely a *v* wave. Read, however, in the light of the other tracings, with their invariably long *a-c* intervals, there is no doubt the interpretation I have indicated by the lettering is the correct one.

Pathological Section. (A. E. C.)

The heart was handed to me by Dr. Griffith, after it had been fixed and hardened by the usual Kaiserling process. Most of the measurements which follow were therefore made after fixation: many however were made by him in the recent state and are here inserted. In supplement to Dr. Griffith's account, detailed description and measurements are given below. Some of the main conditions of the valves, especially in regard to their stenosis and insufficiency in the recent state, are given in the post-mortem description.

There was hypertrophy of the right auricular appendix (its wall being 7 mm thick at the middle), and of the wall of the right ventricle (11 mm. at the auriculo-ventricular opening, 3 mm. at apex, and 5 mm. at the middle of the conus). There was also dilatation of the right ventricle (7.5 cm. from auriculo-ventricular ring to apex and 10.3 cm. from apex to pulmonary valves). The endocardium of the auricle was thickened and whitened, and towards the attachment of the tricuspid valve it became more opaque, in places yellowish white, and thicker—almost cartilaginous in parts. Directly under the attachment of the middle of the mesial flap of the tricuspid valve was an irregular patch (12 × 10 mm.), which raised up the endocardium slightly, was yellowish white, in parts bluish, and very dense. It was the upper portion of this area and a portion just above and behind it which was translucent, and represented the *pars membranacea septi*, an area roughly and irregularly 2 cm. square. The pulmonary valves did not show any abnormality.

The left auricle was dilated and considerably hypertrophied (its wall being 7 mm. thick in the posterior portion). The endocardium was thickened and whitened, and at the auriculo-ventricular ring, especially at the line of attachment of the aortic flap of the mitral valve, presented irregular, yellowish-white, slightly raised, and densely infiltrated tissue. The foramen ovale was closed.

The ventricle was much dilated (10.3 cm. from apex to aorta), the trabeculae being much flattened. The wall was hypertrophied: it measured at the auriculo-ventricular ring on the left side, 13 mm.; at the apex, 5.5 mm.; at the root of the aorta, probably 2 cm. (the wall was cut obliquely). The endocardium of the ventricle was only slightly whiter in the path of exit of the blood current than elsewhere. Markings representing the auriculo-ventricular bundle were not made out, their usual site being also that of the slightly thickened endocardium.

The mitral valve was elongated to a narrow funnel shape, its substance occupying the intervals normally existing between the cordae tendineae and filling out the spaces between them almost to their attachment to the papillary muscles. The substance of the flaps throughout was thicker.

The aortic valve was much deformed. The *anterior flap* was intact, but had just behind the corpus Arantii a nodular thickening 5 mm. in diameter, like the patches already described at the attachment of the mitral and tricuspid valves. In the corresponding sinus of Valsalva was a similar patch, which was puckered in the centre, forming a star-like depression. There was no loss of surface substance. The opening of the coronary artery was normal. The *left posterior flap*, except for marked thickening of the corpus Arantii, showed no abnormality. The *right posterior* valve, however, was entirely transformed. Its diameter from free margin to attachment was 2.7 cm., whereas that of the anterior was 1.2 cm.; and it measured transversely from one attachment to the other 2.5 cm., whereas the anterior measured 1.6 cm. The valve itself was throughout thickened, yellowish white and dense. At its lower portion was a perforation 10 x 11 mm., the edges of which were irregular, the upper margin bluish, while the rest showed the yellowish-white colour already noted. At its attachments to the aorta, to the septum (which attachment was lower than usual by almost 2.5 cm.), and dorsally to the aortic flap of the mitral valve, there was marked thickening, the tissue being of the same colour and character as that already described. A plaque extended from the lateral attachment on the right side 1.4 cm. up into the aorta and was 1.4 cm. wide, with irregular rounded margins. The sinus of Valsalva was correspondingly increased in size, and the orifice in the recent state admitted the first phalanx of the ring-finger. The translucent area described on the right side corresponded to the aortic wall of this aneurysm-like sinus of Valsalva.

It will be perceived that an aneurysmal dilatation of the right posterior sinus of Valsalva had been made, and that the antero-left wall, formed by the cusp of the aortic valve, had been depressed downwards and forwards on the septum so that the septum membranaceum was included in the aneurysmal pouch, the cusp being attached therefore to the lower rather than to the dorsal margin of the membranous septum, as in the normal condition.

In addition to the plaque already described, the aorta presented only slight intimal thickenings. The star-like scars due to disease of the media, so characteristic of syphilis, were not found.

When the normal course of the auriculo-ventricular bundle is remembered (from its commencement in auricular musculature behind, usually under the endocardium of the right auricle, then traversing the interauricular septum to lie under the endocardium of the left ventricle, then passing forward through the membranous septum near its lower portion, dividing into its right and left branches near the anterior border of the same), it will be evident that the distortion of the parts caused by the aneurysmal dilatation of the sinus of Valsalva, which comes to affect the septum membranaceum and convert it into

its right posterior wall, may in some way have disturbed the relations of the auriculo-ventricular bundle. The clinical records seem to point to some such anatomical change. Macroscopically, at all events, the course of the bundle could not here be discerned. Its course and its relation to the membranous septum and to the altered position of the attachments of the aortic valve are reported in the microscopic examination which follows.

Microscopic examination. The portion within the large square, shown in the photographs of both the right and left sides, was excised. This rather large piece was then further divided into four pieces, also indicated, while a fifth piece consisted of the flap of the aortic valve which formed the aneurysmal wall. Each of these pieces was embedded in celloidin-paraffin (the portion marked 1 being first decalcified), and sections cut in a plane at right angles to the long axis of the heart—that is, parallel to the upper margin of the aortic valves. The sections were usually 12–15 micra thick, though in some places (bottom of part 2) 8 micra. For the most part every third section was mounted, occasionally, as in part 2 already mentioned, every section, and in the upper portion of part 1, every fifth section. The stain used was iron haematoxylin and van Gieson.

The course of the bundle is indicated in the photographs of the right and left heart by the white marks. The entire system was at a slightly lower level (by about 3 to 4 mm.) than usual. Had it preserved its normal course at a level below the lowermost attachment of the aortic cusps, the displacement downwards would have been considerable. The aneurysm alone, however, found its attachment at the lowermost level of the pars membranacea septi, leaving the auriculo-ventricular system in place.

The auriculo-nodal junction was well developed, and lay in the interauricular septum in the floor of the entrance of the coronary sinus and at the level of the attachment of the mesial flap of the tricuspid valve. The auriculo-ventricular node itself was large, and showed the usual arrangement. It is separated from the endocardium of the right auricle by a thin layer of auricular muscle.

The main stem was continued from the upper and middle portions of the node and took the usual course through the membranous septum. At the anterior portion it divided into its right and left branches. The right branch was followed very well, first separated from endocardium by connective tissue, and then coming to lie in the interventricular septum. The left branch was followed in its usual situation, its course being more difficult to follow.

In its course from beginning to end, the integrity of the auriculo-ventricular bundle was variously compromised. The large artery which supplies the node, as well as all the vessels of its size in the septum, showed an endarteritis which greatly diminished their calibre. There were some arteries which were entirely occluded. Scattered throughout the interauricular septum, and particularly about the node, though to a less extent within it, were large and small groups of lymphocytes. The lymphocytes within the node were found singly and in small

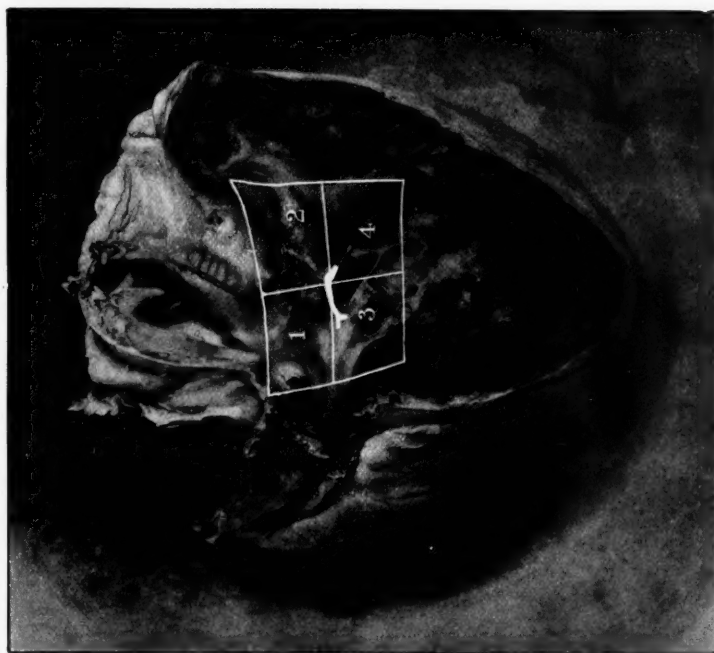
groups. Within the node the connective tissue did not seem to be increased, but to the left and in front where the wall of the aneurysm was formed, the connective tissue was very dense, possessed very few nuclei, and was poorly supplied with vessels. To the right and behind it were a great number of small, thin-walled vessels, closely placed, there being a few lymphocytes scattered in between. This granulation tissue did not seem to compromise the node. As before mentioned, the *main bundle* emerged from the upper and upper middle portions of the node. It passed forward in the median line of the septum, through very dense connective tissue, which was of the same character as that in relation to the node and also formed a portion of the aneurysmal wall. This connective tissue insinuated itself between the muscle bundles of the main stem, so that strands of two or three fibres were separated by masses of connective tissue two or three times their diameter. In portions of the bundle, granulation tissue with lymphocytes, similar to that already mentioned, was found. Although the continuity of the main stem from the auriculo-ventricular node to the point of its division into branches was not interrupted, its diameter was markedly reduced and the individual fibres obviously compressed.

From the point of division the *right branch* was readily followed as a bundle of considerable size. It passed directly behind the plaque on the interventricular septum under the mesial flap of the tricuspid valve mentioned in my macroscopic description, but seemed not to have been compressed by it. As far as the right branch was followed, it was distinguished from the surrounding heart muscle not only by its usual characteristics, but by the fact that it alone was accompanied by lymphocytic infiltration. In the upper portion of its course, this infiltration was very dense, though further downward it became progressively less marked.

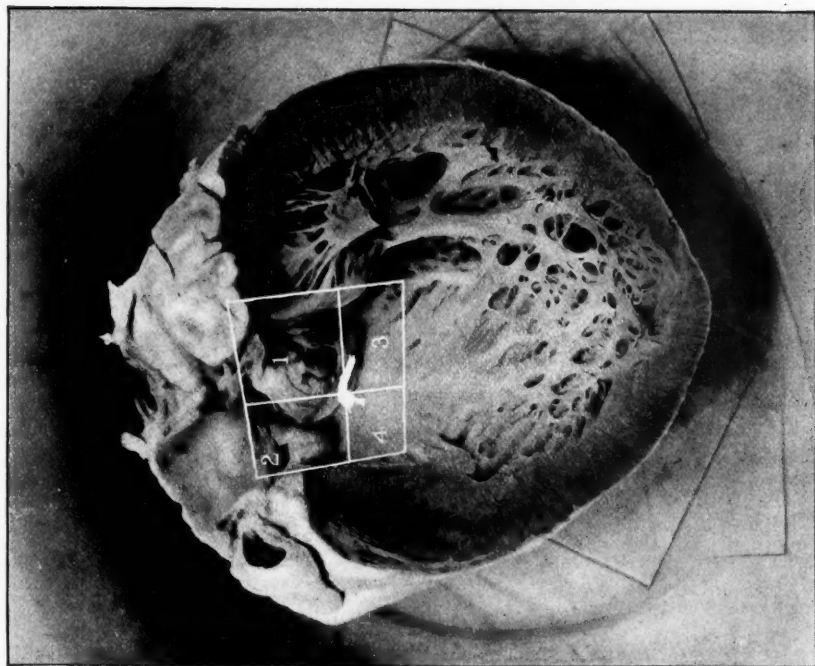
The left branch, also accompanied by lymphocytic infiltration, was followed as a thin strand composed of relatively few fibres. Its course lay directly under the lower lateral attachment of the aneurysmal cusp. The base of the valve was itself the seat of active and also chronic inflammation. There were here large lymphocyte collections, granulation tissue, and dense connective tissue. Through this mass the left branch could be followed for some distance, but then its course was interrupted. At a point lower down in the septum it could again be picked up.

The two plaques specially mentioned, the one at the root of the aorta and the other on the interventricular septum under the mesial tricuspid flap, were both composed of dense masses of connective tissue. The *aortic* plaque contained several vessels completely obliterated by endarteritis. There were likewise lymphocyte collections, though there was no granulation tissue. There was a hyaline degeneration of the muscle caught within it. The nerve bundles which lay further in were seemingly not injured.

It appears, therefore, that in this case the auriculo-ventricular bundle was seriously compromised in its main stem and that the left branch was cut off, but



Interior of right side of heart. The septal segment of the tricuspid valve has been cut in its longitudinal axis.



Interior of left side of heart.

that whatever impulse may have passed through the remains of the main stem may have been propagated along the right branch and so spread to the ventricles. The nature of the lesion itself, the character of the inflammation, the entire absence of leucocytic infiltrations and abscesses, the very marked endarteritis, all speak for syphilis as the causative factor.

The literature of the anatomy of the bundle and the pathology of heart-block are not repeated here. They are found in—

1. Tawara, S., *Das Reizleitungssystem des Säugetierherzens*, Jena, 1906.
2. Mönckeberg, J. G., *Untersuchungen über das Atrioventrikulärbündel im menschlichen Herzen*, Jena, 1908.
3. Nagayo, M., 'Pathologisch-anatomische Beiträge zum Adams-Stokesschen Symptomenkomplex,' *Zeitschr. f. klin. Med.*, lxvii.

A STUDY OF THE CEREBRO-SPINAL FLUID IN THE INFECTIVE DISEASES OF THE MENINGES WITH SPECIAL REFERENCE TO CEREBRO-SPINAL FEVER

By ANDREW CONNAL

With Plate 3

Introduction and Methods of Examination.

THE subject of this paper is an account of a long series of observations on the cerebro-spinal fluid in the acute pyogenic and the tuberculous forms of meningitis. A study of this fluid has been found to give valuable information as regards both diagnosis and prognosis, and promises to equal in importance the examination of the urine in cases of nephritis, or of the blood in the various forms of anaemia. Over one thousand specimens of fluid have been examined. These were taken from cases of acute pyogenic and tuberculous meningitis which occurred mainly in the City of Glasgow Fever Hospital, Belvidere, and in the Royal Hospital for Sick Children, Glasgow. Of the acute pyogenic cases, 152 were due to the meningococcus of Weichselbaum, Fraenkel's pneumococcus was the organism in four, three were caused by streptococci, and two were cases of mixed infection following on fracture at the base of the skull. The cases of tuberculous meningitis numbered sixty-nine. The procedure was as follows:—Lumbar puncture was performed at regular intervals, and each sample of fluid examined along definite lines. Four of the cases were punctured twice a day, twenty-five daily, and twenty-one on alternate days. Single punctures only were made on twenty acute fatal cases. The remaining cases were punctured at intervals of two days or longer. The results obtained from the examination of each specimen of fluid are tabulated in the following manner:—

A. *Physical Characters.* 1. The intracranial pressure. This was estimated either accurately by means of a cerebro-spinal manometer, or, roughly, by observing the rate of flow of the fluid through the cannula, and by the quantity of fluid obtainable without harm to the patient.

2. The degree of turbidity. This is classified under headings of 'clear', 'opalescent' and 'turbid'.

3. The colour. This character is described as 'colourless', 'white', 'yellow', 'green', or 'brown'.

4. The consistence. The fluid is of a watery nature in most of the specimens. In a number of cases thick gluey pus is obtained. Gradations between the two are rare, but in some cases the fluid possesses adhesive qualities,

resembling an inflammatory pleural effusion of a slightly opalescent or nearly clear appearance.

5. The specific gravity. For this purpose a hydrometer, specific gravity bulbs, or a weighing bottle were used.

6. The coagulum. The amount, the character, and the time of appearance of the clot were noted, and the distinctions drawn are 'coarse cobweb', 'fibrillar', and 'woolly'.

7. The amount and the character of the sediment.

B. Chemical Tests. 1. The reaction. This was tested by litmus paper or by phenolphthalein.

2. The amount of albumin. This was estimated by Esbach's apparatus.

3. The presence or absence of (a) sugar, (b) lactic acid, (c) phosphates, (d) urea, (e) choline.

C. Microscopical Characters. 1. (a) The relative numbers of the different forms of leucocytes. Differential counts were made of the polymorphonuclear and the mononuclear cells. (b) The degree of degeneration in these cells as shown by their appearance and their staining properties.

2. The presence of endothelial cells.

3. The causative organisms, their number and their situation, whether extra-cellular or intracellular.

4. The varieties of crystals.

Determination of the day of illness. With regard to the cases of cerebro-spinal fever, the day on which headache, sickness, and vomiting occurred is taken as the day of onset of the disease. The last sign, in a long series of cases, was found to be the most reliable, as being the earliest and most constant feature in connexion with the onset of illness. In the great majority of the cases of tuberculous meningitis, however, it was found impossible to obtain similar definite information. The history elicited was usually one of insidious onset, and accordingly all the cases have been dated backwards from the day of death.

General considerations. The method of performing lumbar puncture is too well known to require detailed description, but several points of practical importance are worthy of note. The patient is placed on his right side, with the knees drawn up and the left shoulder inclined forwards so that the lumbar concavity is straightened out. This position gives the operator the best advantage if he be naturally right-handed. If the patient be an adult, it is desirable to have two assistants, but a child can easily be managed by one. A well-tempered, sharp-pointed, hollow, steel needle is used. For an adult the needle should be at least three inches in length and the diameter of the lumen $\frac{1}{16}$ of an inch. For a child, a proportionately smaller needle is necessary. Thus, under the age of two years, one about two inches in length and $\frac{1}{32}$ of an inch in diameter is most suitable. The spinal canal

is best entered directly in the middle line, between the spinous processes of the third and fourth lumbar vertebrae. When punctures are made daily it is better to enter the interspace above or below the seat of election, at intervals, so that undue irritation to the parts may be avoided. A firm thrust in a slightly upward direction is nearly always successful in entering the spinal canal. Too much force must not be used, otherwise the needle will impinge on the body of the vertebra and cause bleeding. If the needle become blocked it is easily cleared by means of a stilette: suction is not necessary. Even thick pus flows out when the needle is clear and inside the dural sac. The operation, if quickly and successfully performed, causes only momentary pain. On two occasions lumbar puncture has been carried out and fluid collected without awakening the patient from sleep. In several other instances, babies, a few months old, placidly sucked at the feeding-bottle during the operation. Throughout the whole series of punctures it was never found necessary to administer an anaesthetic, either local or general. When enough fluid has been collected, the thumb should be kept over the end of the canula on withdrawal, to prevent the infected fluid entering the tissues. In one case a small abscess formed over the site of the puncture, which was possibly due to this cause. If fluid be not obtained, even after clearing the lumen with a stilette, manipulation of the needle should be avoided, as discomfort as well as bleeding are likely to ensue. In this case the needle should be at once withdrawn and re-inserted lower down or higher up.

Three dangers of a grave nature are associated with the procedure. Either too much fluid may be withdrawn, at the risk of shock and collapse, or sepsis may be introduced and a mixed infection result. These two are eminently avoidable, and the second did not occur in the present series of cases. As regards the first, in only one case did collapse follow the withdrawal of fluid. The patient in this instance was a boy suffering from cerebro-spinal fever, on the second day of the disease. He was very acutely ill, and was delirious. There was considerable struggling during the operation. Only three drachms of fluid were collected, but within a few minutes he showed signs of collapse—pallor, cold extremities, and weak rapid pulse. He recovered quickly, and it was thought that his condition might have been due to exhaustion from his own efforts. The third danger arises from the possibility that the withdrawal of fluid may cause a re-infection from a quiescent focus. The withdrawal of fluid under high pressure, sufficient to reduce the intracranial tension to a subnormal point, may set up an increased flow, by which infective material is carried from a circumscribed exudate and deposited in a fresh seat. It is impossible to say whether or not this accident ever happened, but in no case was a relapse or a recrudescence traced to this cause.

Apart from the danger to life, several other accidents may happen. The disadvantage of causing bleeding has already been mentioned. Damage may be done to the nerve filaments in the cauda equina. Severe cramp in the legs, probably due to this occurrence, was experienced by two patients. Other two

patients complained of an intense desire to defaecate. In young children under two years of age, evacuation of the bowels and voiding of urine took place in several instances, but they may have been involuntary acts due to pain or fright. Slight sickness, headache, and increased rapidity of the pulse were observed in a small number of the cases. In only one case did actual vomiting occur. In two instances a certain amount of oedema, probably from leakage through the dural puncture, resulted at the site of the operation. The experience of other observers has been somewhat similar. Chauffard and Boidin performed lumbar puncture in 233 cases. Vomiting occurred in three out of the total, and no other adverse symptom was noticed. They advocate the median method of puncture in order to avoid haematoma, which occurred in two of their cases. Silva prefers the sitting posture for puncture. He states that fatal accidents are rare and occur mainly in cerebral tumour, and that minor disturbances such as vertigo, vomiting, headache, and syncope may be avoided by withdrawing the fluid slowly through a fine cannula, never using aspiration.

The Effects of Lumbar Puncture.

Lumbar puncture was performed in order to verify the diagnosis on every case sent in as cerebro-spinal fever to Belvidere Hospital. It proved at the same time of such value as a therapeutic measure that it replaced the use of chloral, opium, and other sedatives to a great extent. Headache and backache were effectually relieved in many cases by the withdrawal of a few drachms of fluid. The most striking instances of the relief afforded occurred in the early stages of acute cerebro-spinal fever. The first puncture generally afforded more marked relief than subsequent punctures. The operation did not have the same effect in all the cases. Some patients stated they were not benefited at all. Such patients as were improved by the first puncture were always relieved by the same procedure at later stages of the disease. An illustrative case is that of M. H., aged 22 years, who suffered from tuberculous meningitis. This patient as a rule complained of severe headache, and became very restless towards night. When this happened, lumbar puncture was performed. The first effect of the withdrawal of fluid was always the aggravation of the pain even to the extent of agony, but almost immediately afterwards the patient fell into a sound and restful sleep lasting six or eight hours. Within a varying interval after waking, however, the restlessness and headache gradually returned, when lumbar puncture again gave relief. The maximum amount of fluid which the patient could suffer being withdrawn was six drachms. The complaint that the headache became worse during the withdrawal of fluid was common, and was usually made when about four drachms had been collected. This aggravation of the headache was not observed in all the cases, but it always recurred during subsequent punctures in the same patient.

The withdrawal of more than six drachms of fluid in the early stages of cerebro-spinal fever was deemed unwise. Increased rapidity of the pulse was

noticed in some of the cases when a larger amount was collected. In the chronic cases, however, as much as two ounces of fluid have been withdrawn without apparent ill effect. The withdrawal of fluid from the spinal canal frequently lessened the retraction of the head. This improvement was specially noticeable in Case X. This patient was admitted on the second day of illness, when retraction of the head and opisthotonus were well marked. After the withdrawal of four drachms of turbid fluid on the evening of admission, the contracted neck muscles relaxed considerably. On the following morning, the arching of the back had disappeared and the head moved with some freedom.

Frequent lumbar puncture is of service in the later stages of cerebro-spinal fever when hydrocephalus tends to develop. The regular withdrawal of eight or twelve drachms of fluid appears to be of benefit in some instances. The operation probably lessens the tendency to pressure-atrophy of the brain which follows the distension of the cerebral ventricles, while the diminution in pressure also aids in re-establishing the normal processes of circulation in the damaged blood-vessels and lymphatics. Case CXII is illustrative. This patient was admitted on the twenty-first day of illness, with all the signs of cerebro-spinal fever. The fluid was turbid, the polymorphonuclear percentage was 90, the albumin measured two grammes per litre, and the organisms were abundant and mainly intracellular. By the fifty-fourth day of illness the physical condition of the child pointed to the presence of hydrocephalus. Macewen's tympanitic note on percussion of the skull was present, there was prominent bulging of the anterior fontanelle, and the eyes were staring. The pus cells in the fluid were 18 per cent., the albumin was estimated at $3\frac{1}{2}$ grs. per litre, the intracranial tension was greatly increased, and the fluid itself was slightly opalescent. At this time daily lumbar puncture was instituted, and amounts varying between one and two ounces of fluid were withdrawn. After two days slight turbidity of the fluid reappeared, the albumin measured $4\frac{1}{2}$ grammes per litre, and the intracranial tension remained high. On the fifty-ninth day of illness the fluid was almost clear again, but although no organisms were seen in the stained film, the culture was positive. Next day the culture was negative and it remained so. From this time (sixtieth day) onwards a steady improvement was observed, and when the daily lumbar punctures were discontinued, on the eightieth day of illness, the fluid, although still under considerable pressure, was clear, the albumin measured one gramme per litre, and the cells were entirely mononuclear. On the 116th day there was no coagulum, and the albumin amounted to only half a gramme per litre. The staring look had gone and the anterior fontanelle was normal. The circumference of the head was measured from time to time. When the daily punctures were begun the measurement was $17\frac{1}{2}$ inches. A fortnight later it was 17 inches, and when the punctures were stopped the measurement was $16\frac{1}{2}$ inches. The child was dismissed well, and a year later she appeared to be normally bright and had learned to speak.

Silva found that lumbar puncture was always successful in chronic hydro-

cephalus and not rarely led to cure. His best results occurred when, after the withdrawal of fluid from the spinal canal, the depression of the anterior fontanelle persisted for four to ten hours.

The Intracranial Pressure.

An increased intracranial pressure occurs in all forms of meningitis. Under normal conditions the cerebro-spinal fluid issues from the hollow needle in slow or rapid drops, except in the case of young children, when a rapid stream or even a jet of short duration may occur. The rate of flow is increased both in normal and diseased conditions by rapid or forced respirations, compression of the anterior fontanelle, constriction of the vessels in the neck, or by pressure on the abdomen. In meningitis there is either a continuous stream or a more or less powerful jet. Two exceptions occur. In the late stages of hydrocephalus the distension of the cerebral ventricles may be so great that the brain substance is everywhere tightly pressed against the cranial walls, and the communication with the spinal cavity is completely cut off. In this condition only a few drops of fluid can be obtained. The case of J. McG., aged $1\frac{1}{2}$ years, is illustrative. This patient was admitted on the forty-first day of illness, quite unconscious, in a state of advanced emaciation with considerable rigidity. The anterior fontanelle was bulging prominently. On the forty-sixth day the fluid issued from the cannula in rapid drops, but less than three drachms were obtained. Four days later, at the post-mortem examination, the cerebral ventricles were found enormously distended and the brain substance glued against the dura mater lining the cranial cavity.

Shortly before death in the chronic forms of cerebro-spinal fever, and in tuberculous meningitis, the fluid may come only in very slow drops, the decreased arterial pressure and the general loss of tone probably accounting for this agonal phenomenon. An apparent exception also exists in cases where the fluid is thick and purulent so that it flows with difficulty through the cannula, but in such cases a large amount can always be collected. Blocking of the cannula accounts in other cases for a tardy flow of fluid.

The intracranial pressure is greatest in the early stages of acute cerebro-spinal fever. During the first few days of illness the pressure may be so great that the fluid spurts high out of the needle. As the acute symptoms subside the pressure gradually falls, although the fluid is still under a high pressure for some time after the temperature becomes normal. The onset of hydrocephalus causes the intracranial pressure to rise again, and this occurrence is a significant indication in the later stages of the disease. In tubercular meningitis the initial intracranial pressure is also above the normal, and it continues to increase gradually as the disease progresses. For all practical purposes the amount of intracranial pressure can be sufficiently well judged by the rate of flow of the fluid. Eve's cerebro-spinal manometer was used in the earlier cases of

the series, as it had the advantage of recording the pressure both before and after the withdrawal of fluid, so that the risk of collecting too large a quantity was diminished. The instrument consists of a vertical glass tube affixed to a metal framework which is marked off in inches. India-rubber tubing connects the cannula with the glass tube. 'The pressure is recorded in terms of a column of water, when the zero mark is held at the level of the site of puncture.' Twenty-four cases of tubercular meningitis and twelve of acute pyogenic meningitis were accurately measured with this instrument, forty-three observations being made. The greatest intracranial pressure was observed in a case of acute cerebro-spinal fever on the first day of illness. The fluid at the commencement rose beyond the range of the manometer, that is, over 24 inches. When three drachms had been withdrawn, the reading was 18 inches. The next highest reading was also in a case of acute cerebro-spinal fever, on the fifth day of illness, when the height of the fluid was 22 inches. In the tuberculous cases the highest pressure was in a patient five days before death, when the column measured $17\frac{1}{2}$ inches. In other two cases punctured three days before death, the fluid rose to $16\frac{1}{2}$ inches.

The level of the fluid was observed in most of the cases to fluctuate with the pulse and with the respirations, small and rapid variations synchronizing with the pulse-rate, and larger and slower alterations with the breathing. The limits of variation with the heart-beats were one-eighth to one-quarter of an inch, and the respirations usually caused a difference of from one to three inches. In one case, L. H., aged 11 years, on the seventieth day of illness (cerebro-spinal fever), when marked hydrocephalus was present, the patient was taking short rapid inspirations and prolonged expirations, terminating in a groan. The height of the fluid was greatest in the middle of the expiratory period; the level began to fall when the groan came on, was still falling during inspiration, and began to rise immediately and rapidly with expiration. The fact is known that expiration causes a flow of fluid through an opening in the cranium or spinal canal, and that the fluid recedes with inspiration. The peculiar breathing of the patient in the above instance permitted an accurate observation of the phenomenon. The height of the fluid was raised $5\frac{1}{2}$ inches, in one case, by pressure on the abdomen. Compression of the anterior fontanelle in another case, and the act of crying in a third, increased the height 5 inches. Twelve inches of an increase were observed in a fourth case during struggling. In two instances, after more than an ounce of fluid had been withdrawn, air was sucked into the spinal canal during inspiration, the fluid coming out aerated with the next expiration. Both of these cases recovered.

Observations were made in a case of tuberculous meningitis with a view to finding the rate of the reaccumulation of the fluid. At the first puncture the height was 15 inches. After eight drachms had been withdrawn the height was $4\frac{3}{4}$ inches. Two hours later the pressure was equal to $7\frac{1}{2}$ inches, and when two drachms of the fluid had been collected the height was 4 inches. Five hours after the first puncture (three hours after the second) the height was 10 inches.

A STUDY OF CEREBRO-SPINAL FLUID IN MENINGITIS 159

The amount of fall in intracranial pressure raises the question whether the pressure was due to excess of fluid or to the congestion of the tissues. A decided fall, consequent on the withdrawal of a large amount of fluid and followed by

TABLE I.—Showing height in inches to which the fluid rose in the manometer.

Tuberculous Cases.

Case.	Last Day.	Day before Death.									
		2nd.	3rd.	4th.	5th.	6th.	7th.	8th.	9th.	10th.	11th.
LVII	15½										
LVI	4	15									
XLVI	11½										
XVIII	4½										
II	13½										
I		15	11								
XVII		21									
LIV	15½										
XLII	11½										
XLVIII	4½										
LVIII			16½								
XXIV			16½								
XLVII				6½							
VI				16							
XLI				11½							
XXXIII				11							
XV				5½							
LIX					17½						
XXXII					11						
X					16½						
XXIII							11½				
XXII										13½	
III										5½	

Cerebro-spinal Fever Cases.

Case.	Day.							Week.									
	1st.	2nd.	3rd.	4th.	5th.	6th.	7th.	2nd.	3rd.	4th.	5th.	6th.	7th.	8th.	9th.	10th.	
CXXI	18																
CXXII		9½															
CXXIII			11														
CXXIV				8½													
CXXV					22			11									
CXXVI								12½									
CXXVII									6½								
CXXVIII											9						
CXXIX										13	11						
CXXX																	
CXXXI																9	
CXXXII																10	

relief to the patient, would indicate that the fluid itself, formed in excess or unable to find exit by the usual channels, was the cause of the increased pressure. Conversely, a slight lessening of pressure, when only a small amount

of fluid was obtainable and with no relief to the symptoms; would suggest that the congested state of the tissues themselves occasioned the high pressure. This was found to be so.

In the present series, the points attended to were the initial pressure, the amount of fluid withdrawn, and the final pressure. The manometric readings are given in Table I. The fall of pressure in inches was divided by the amount of fluid collected, in drachms, and it was thought that this figure would correspond in similar cases. To a certain extent, some agreement was observed, but there are various pathological and physiological influences which are imperfectly understood, and these, along with the effect of the mental and physical state of the patient at the time of puncture, modify the interpretation of the results considerably. It was definitely found, however, that in acute pyogenic meningitis the swelling of the nervous tissues, which is considerable, is accompanied by exudation of fluid, more or less great, so that both causes operate in raising the pressure, unless in the late stages of the disease, when a great excess of fluid has formed, causing thinning of the brain matter. In tuberculous meningitis, on the other hand, as the disease progresses, the excess of fluid in the ventricles and in the subdural space becomes in increasing ratio the cause of the abnormal pressure.

From the post-mortem records, the greatest congestion of the brain and cord was noted in the cases of acute cerebro-spinal fever, and internal hydrocephalus was always most marked in the chronic stage of that disease. In tuberculous meningitis, external hydrocephalus was more often present and was greater in degree than in the acute pyogenic cases.

The Turbidity.

The normal cerebro-spinal fluid is clear. Any departure from this transparency is pathological, unless bleeding has been caused by the needle in entering the spinal canal, in which case a more or less pink opalescence may occur. A turbid appearance is due to the presence of leucocytes, endothelial cells, organisms, shreds of fibrin, and granular detritus. When the fluid is first collected these matters are in suspension and the turbidity is uniform. Rapid sedimentation follows if the fluid be very turbid, but, as a rule, a coagulum forms ere much sediment has collected. This clot, which entangles the suspended matters in its meshes, gradually sinks to the bottom of the test-tube, leaving the supernatant fluid of an opalescent appearance. The opalescence may be still further reduced by centrifugalization. In the present series four main types of exudate are described:—(1) thick pus; (2) turbid fluid; (3) opalescent fluid; (4) nearly clear fluid. The term 'pus' is used when thick gluey material alone, which flows with difficulty through the cannula, is obtained by lumbar puncture. A turbid fluid is one which contains more or less particulate matters very similar to the flocculent deposit which forms on boiling a urine heavily loaded with albumin. An opalescent fluid appears like water to which a few drops of milk have been added, and the term 'nearly clear' is applied to a fluid which only appears slightly hazy on being compared with distilled water.

These terms have been chosen because each represents a distinct stage of cerebro-spinal fever, and, so far as is known, no attempt has been made by other observers to make a classification of this kind. Each variation in the appearance of the fluid has a definite significance with regard to the clinical course of the disease, and to the other conditions in the cerebro-spinal fluid itself. In a case of cerebro-spinal fever which recovers there is a more or less marked turbidity of the fluid in the early period of the illness. As the disease subsides the fluid becomes opalescent, until finally the normal translucency is regained. This is regarded as the proper sequence of events, but in the majority of cases the disease is characterized by remissions, and these are evidenced by a reappearance of the turbidity or by a more decided opalescence.

A turbid fluid always indicates an acute pyogenic meningitis. The turbidity makes its appearance very early in the disease. In one case it was markedly present within eight hours of the onset of the illness. In general, it may be said that turbidity is well established within the first twenty-four hours. It will be seen that on the first day of illness an opalescence is the commonest appearance, and by the end of the first day turbidity is decided. The turbidity persists during the first week of illness. In the second week the fluid is generally only slightly turbid, and during the third week an opalescence is most often present. These changes in the appearance of the fluid are characteristic of the most common type of the disease, in which the illness continues acutely for about three weeks and then proceeds to recovery or to become chronic.

Two cases out of the three examined early on the first day of illness showed a decided opalescence of the fluid, and the other was turbid. Two cases examined twenty-four hours after the onset presented a very turbid fluid. A marked degree of turbidity was present in seventeen out of eighteen cases which were punctured on the second day of illness. The exception was a patient (Case XVI) who was admitted on the second day of the disease. He was very acutely ill and he died on the seventh day. The course of the illness was atypical in many ways. Punctures were made on the second, third, and fourth days, and at no time did the fluid show more than an opalescence. Seventeen specimens were examined on the third day of illness and, with the exception already noted (Case XVI), turbidity was present in them all. Twenty-five cases were punctured on the fourth day of illness, and all the fluids were turbid except in Case XVI already noted, and in Case XXXIX, where there was thick gluey pus. From the fifth day onwards, variations in the appearance of the fluid become more numerous. The earliest day on which thick gluey pus appeared was noted as the fourth day of illness. It was most frequently observed during the second week of illness, and the latest date of its occurrence was the forty-third day of the disease. The earliest day on which opalescence succeeded turbidity was noted as the fifth day (Case XXXIV). This patient was admitted on the third day of illness with a very turbid fluid. An opalescence was observed in only one other case on this day of the disease out of the total 35 which were punctured. The patient (Case LIV) had not been under observation previously. The

turbidity, on the other hand, may persist for long periods, or reappear after considerable intervals. In Case CXI a decided turbidity was present on the 111th day of illness. During the whole course of the disease in this patient the fluid had never cleared, opalescence and turbidity alternating throughout until death on the 179th day. A close relation is exhibited between the severity of the symptoms, the degree of pyrexia, and the amount of turbidity, and each in a measure is an index of the others. In the acute cases with an early fatal termination the temperature as a rule is high and the turbidity is great. In a small number of these cases the illness is prolonged for about ten days and the turbid fluid is succeeded by thick pus. Exceptionally, a very acute case occurs in which the temperature is normal or subnormal, although the fluid is very turbid. In the acute, critical, or abortive cases, which terminate within about fourteen days in recovery by a crisis, the fluid clears almost as rapidly as the temperature falls. Those forms of the disease which have a long period of chronicity, ending either in recovery or death, show the same accordance of the turbidity and temperature curves, although less uniformly. The onset of these cases may be either acute or subacute, with a turbid fluid which may change into thick pus. Each increase of pyrexia during the chronic stage in such cases is accompanied by a more or less decided turbidity, and the intervals of apyrexia synchronize with a clearing up of the fluid. This correlation was found to be practically constant, and it illustrates that the temperature as a guide to the progress of the disease is especially reliable in the acute phases.

In a number of the cases the fluid was drawn off in two or more portions. It was thought that by examining these separately, a rough estimate of the extent or of the site of the lesion might be arrived at. This procedure was adopted in thirty-six cases, but a difference in the degree of turbidity between the first and the second specimens was only observed in three. Details of these cases are given.

Case CVIII. On the sixteenth day of illness the second sample was the more turbid. At the post-mortem examination on the following day, more recent pus was found on the vertex than at the base of the brain or on the cord. It is suggested that the greater turbidity in the second sample indicated that the brain was the more affected.

Case XXXIV. The second sample was the more turbid on the eighteenth and twenty-second days of the illness. At the post-mortem examination on the twenty-seventh day, the cord was found to be free from pus, while the exudate at the base of the brain was abundant, and pus was extending up the Sylvian fissures. Here it is suggested that the greater turbidity in the second sample indicated the vertical extension, and the greater involvement of the brain than of the cord.

Case LXXXVI. The second sample on the fourteenth and sixteenth days of the disease was less opalescent than the first. This patient had a mild attack ending in recovery. The significance of the greater opalescence in the first sample was thought to be that the exudate was clearing up rapidly, and the first

sample contained the debris which had gravitated to the bottom of the dural sac. The second sample, coming from higher up, was consequently clearer.

Case XC. Two samples were taken on the eighth and ninth days of illness, and three samples on the tenth. Turbidity was very great, and was equally marked in them all. At the post-mortem examination on the following day an extensive vertical and basal meningitis was found and the cord was bathed in pus. It is suggested that the equal turbidity in the specimens on each occasion indicated the extensive infection. This patient suffered from a septic meningitis following on fracture at the base of the skull. The case is quoted as typical of several in which the diagnosis of a general involvement of the brain and cord was made from the similar appearance of the different samples of fluid. The relationship of turbidity to the pathological conditions will be seen in Table II, where the post-mortem appearances are compared with the characters of the cerebro-spinal fluid at the final puncture during life. A very decided yellowish turbidity is associated with a recent and extensive infection of the cord. If the turbidity be less marked and of a white colour, it indicates either an extensive exudate in which organization is progressing or a lesion confined more or less to the base of the brain. An opalescent fluid at a late stage of the disease is characteristic of hydrocephalus, with persistence of some exudate at the base of the brain.

A turbid fluid was never once met with in tuberculous meningitis, and only in one case out of the total 69 did even a decided opalescence occur. It is worthy of note that in this case the opalescence was associated with an abundance of cells, a high percentage of polymorphonuclear cells, and a fair amount of coagulum, on the three occasions on which the fluid was examined. All the other fluids are classified as 'slightly opalescent' or 'nearly clear'. The slight haziness in the majority of cases is only detected when the sample is compared with a similar quantity of pure water.

Table IX shows the appearance of the tuberculous fluids on each day before death. It will be noticed that the fluid tends to become less clear as the disease advances.

TABLE II.—Comparing the appearance of the fluid at the final lumbar puncture with the conditions found at the post mortem.

Name.	Age.	Date of last Lumbar Puncture.	Date of Post mortem.	Degree of Turbidity.	Condition of Spinal Cord.	Condition of Brain.
E. G.	6	22.4.07	24.4.07	Turbid	Not examined	Large hæmorrhages; no actual pus
S. N.	3	23.4.07	25.4.07	Very turbid	Free	Vertex plastered with pus, exudation at base; purulent fluid in ventricles
W. M.	1½	26.4.07	27.4.07	Opalescent	Hyperæmic	Hyperæmic; no pus
B. McG.	1½	6.5.07	10.5.07	Pus	Posterior surface plastered with pus	Exudate at base and on vertex; purulent fluid in ventricles
A. P.	15	8.5.07	10.5.07	Yellow turbid	Pus on posterior surface	Pus at base spreading up the Sylvian fissures
Mrs. T.	44	9.5.07	14.5.07	Yellow turbid	Pus on posterior surface	Pus at base; purulent fluid in ventricles
T. N.	21	12.5.07	17.5.07	Opalescent	Traces of exudate on posterior surface	Pus on vertex and at the base

TABLE II—*continued.*

Name.	Age.	Date of last Lumbar Puncture.	Date of Post mortem.	Degree of Turbidity.	Condition of Spinal Cord.	Condition of Brain.
W. L.	7	17.5.07	18.5.07	Yellow turbid	Exudate on posterior surface	Pus on vertex and at the base
J. McG.	1 $\frac{3}{12}$	16.5.07	20.5.07	Nearly clear	Free	No exudate; enormous distension of ventricles
D. D.	13 $\frac{6}{12}$	18.5.07	21.5.07	Turbid	Free	Exudate at the base
T. R.	13	4.5.07	24.5.07	Very turbid	Exudate on whole extent	Exudate at the base
A. D.	4 $\frac{1}{2}$	2.6.07	3.6.07	Yellow turbid	Plastered with pus	Pus at base and on vertex
E. G.	3 $\frac{1}{12}$	2.6.07	4.6.07	Opalescent	Exudate on posterior surface (organized)	Great distension of ventricles; organized exudate at base
C. McF.	2 $\frac{1}{3}$	4.6.07	6.6.07	Turbid	Small area of exudate in cervical region	Two small areas of recent exudate on vertex; turbid fluid in ventricles
H. E.	7 $\frac{7}{12}$	10.6.07	11.6.07	Nearly clear	Free	Excess of fluid in ventricles
Mrs. C.	38	11.6.07	13.6.07	Very turbid	Not examined	Abundant vertical and basal pus
R. J.	23	14.6.07	17.6.07	Yellow turbid	Bathed in pus	Pus on vertex; scanty pus at base
K. G.	10	26.6.07	29.6.07	Nearly clear	Not examined	Exudate (old) at base; distension of ventricles
Mrs. A.	33	6.7.07	9.7.07	Yellow turbid	Not examined	Pus on vertex and at base
J. M.	4	8.7.07	11.7.07	Yellow turbid	Pus on posterior aspect	Pus on vertex and at base; turbid fluid in ventricles
J. S.	45	30.7.07	1.8.07	Turbid	Firm exudate on whole extent	Pus on vertex and at base
J. C.	3 $\frac{3}{4}$	29.7.07	5.8.07	Opalescent	Free	Ventricles distended
J. McL.	25	9.8.07	13.8.07	Opalescent	Not examined	Pus on vertex; organized exudate at base; ventricles distended
E. McL.	10	14.8.07	19.8.07	Nearly clear	Free	Ventricles greatly distended
R. C.	17	21.8.07	26.8.07	Turbid	Not examined	Vertical and basal pus
C. K.	35	10.9.07	11.9.07	Yellow turbid	Surrounded by exudate	Vertical pus; exudate at base
H. S.	19 $\frac{1}{2}$	22.9.07	24.9.07	Pus	Posterior surface plastered with pus	Vertical and basal pus
M. McN.	34	10.10.07	11.10.07	Turbid	Free	Vertical and basal exudate
J. A.	48	16.10.07	18.10.07	Opalescent	Organized exudate on posterior surface	Scanty vertical pus; exudate at base; ventricles distended
T. R.	11 $\frac{1}{2}$	13.11.07	14.11.07	Very turbid	Patchy areas of exudate	Extensive vertical and basal pus
J. B.	8	20.11.07	22.11.07	Green turbid	Bathed in pus	Vertical and basal pus abundant
W. B.	22	12.12.07	14.12.07	Yellow turbid	Bathed in pus	Vertical and basal pus
J. T.	1 $\frac{1}{4}$	11.1.08	13.1.08	Yellow turbid	Plastered with pus	Vertical pus; firm exudate at base
J. A.	17	13.1.08	14.1.08	Slightly turbid	Free	Firm exudate at base; pus spreading up Sylvian fissures
G. W.	7 $\frac{5}{12}$	10.1.08	17.1.08	Opalescent	Free	Old exudate at base; ventricles greatly distended
M. B.	9 $\frac{0}{12}$	26.2.08	4.3.08	Slightly turbid	Patchy areas of exudate	Organized exudate on vertex and at base
J. D.	23	24.2.08	13.3.08	Nearly clear	Free	Traces of exudate on cerebellum; ventricles greatly distended

The Colour.

Several varieties of colour occur. A greenish-yellow or canary yellow appearance is seen in the fluid from acute cases of cerebro-spinal fever, and it is always associated with a marked degree of turbidity. This colour is not due entirely to the matters in suspension, as, after the fluid has been centrifugalized, a faint tint of yellow or green remains. A milky-white appearance is met with in the less acute cases, when the suspended matters are very fine. The term 'milky', which is commonly used in this connexion, has been discarded in favour of 'white turbid', so that the well-marked difference between 'yellow turbid' on the one hand and 'opalescent' on the other may be brought out. The yellow colour associated with great turbidity was always found to indicate that stage of the disease when pus is being actively and extensively formed. The white turbidity, on the other hand, appeared when the exudate was beginning to be organized, or when the inflammatory process was of a mild nature. Opalescent fluids are usually greyish-white in appearance, and nearly clear fluids are colourless. A straw-colour, a reddish brown, and an olive tint are observed in various fluids in certain conditions:—

1. Where bleeding has been caused at a previous puncture.
2. Where the inflammatory process is of an acute haemorrhagic nature, associated with a somewhat viscid fluid containing a high percentage of albumin. This condition will be more fully described under another section. These different colorations are observed mainly in opalescent or nearly clear fluids, and are due to the alterations occurring in the haemoglobin present in the fluid. The significance of the appearance in the first class was found to be of little importance, but in the second it was very grave.

The tuberculous fluids are uniformly colourless except under the circumstances detailed above, when tints due to the alterations in the haemoglobin are observed.

The Consistence.

Most of the specimens of fluid possess a low degree of viscosity very similar to water. The commonest exception is thick gluey pus which issues in slow drops from the cannula. It is in this sense that the term 'pus' is used in these observations. Some authors describe a 'purulent fluid', but the expression 'a yellow turbid fluid' is better adapted to emphasize the difference between this and actual pus. In the latter condition the material flows slowly, while in the former it flows out almost as rapidly as normal fluid.

The change from a turbid fluid to pus was observed in ten cases, nine of which died. Other four cases, admitted after the first week of illness,

yielded pus on every occasion on which lumbar puncture was performed. All of these patients died. Other three cases in which pus was present were admitted at a late stage of the disease. Two of these cases recovered, the pus having given place to a turbid fluid at the second puncture.

Occasionally it was found that after about a drachm of pus had issued in slow drops from the cannula, it was succeeded by a turbid fluid. It was considered that this occurrence was due to the sedimentation of suspended matters to the lowest portion of the dural sac, and these cases are not included among those noted as yielding pus. In six out of the nine cases where a turbid fluid altered into pus, the pus changed to a turbid fluid again at a later stage of the disease. One of these cases recovered, but the prognosis is very grave when actual pus is obtained.

A condition which is not found described in the literature has been met with in a few cases. A somewhat viscid fluid resembling the inflammatory secretion found in a pleural effusion was noted in seven cases of cerebro-spinal fever and in three cases of tubercular meningitis. Four out of the seven acute cases were adults, of whom three died, and two were children, of whom one recovered. The earliest day of its appearance was the fifth day of illness. In four cases it was first observed on the 13th, 13th, 15th, and 17th days of illness severally. In the remaining two instances it was first noted on the 34th and 41st days of illness respectively, but in one of these cases the lumbar punctures had been discontinued after the first fourteen days of illness, and as the existence of the condition was only observed when the punctures were resumed, it may have been present at an earlier date. The viscosity in this type of fluid was greater than that of water but less than that of pus. It closely resembled blood serum, and it was invariably associated with a slight degree of opalescence, a brownish, yellowish, or olive tint, an abundant early jelly-like clot, and a very high percentage of albumin. Prior to its occurrence, a turbidity had been present in all the cases. Table III gives the details of each case. The colour of the fluid suggested altered blood-pigment. Similar colorations have been observed in fluids drawn off a few days after a previous puncture had caused bleeding, with this difference, that the viscosity, the peculiar coagulum, and the high percentage of albumen were absent. It is justifiable to assume, in these circumstances, that the condition is due to an acute haemorrhagic inflammation with plastic exudations.

The three cases of tuberculous meningitis in which the phenomenon occurred were all severe types of the disease, with a rapid course. Two of the patients were adults, and the viscid condition was present at every puncture during the week before death occurred. The third patient was a child, and only on the day of death was the viscosity observed. These cases are also detailed (Table III).

TABLE III.—Details of seven cases of cerebro-spinal fever and three of tuberculous meningitis, in which the fluid was viscid.

Case CXIII. Cerebro-spinal fever. Age $\frac{6}{12}$. Duration of illness, 40 days. Recovery.

21st day. Polynuclears 93 %; opalescent; shreddy clot; Esbach 1; organisms not seen; cells degenerated; endothelials abundant.

23rd day. Polynuclears 90 %; opalescent; shreddy clot; Esbach 1; organisms intracellular and abundant; cells mixed; endothelials abundant.

25th day. Polynuclears 91 %; turbid; coarse clot; Esbach $1\frac{1}{2}$; organisms intracellular and scanty; cells degenerated; endothelials abundant.

27th day. Polynuclears 90 %; slightly turbid; coarse clot; Esbach $2\frac{1}{2}$; organisms abundant and intracellular; cells mixed; endothelials scanty.

33rd day. Polynuclears 94 %; thick pus; coarse clot; cells mixed; organisms abundant and intracellular; endothelials scanty.

36th day. Polynuclears 88 %; pus; coarse clot; cells mixed; organisms, extra-cellular scanty, intracellular abundant; endothelials abundant.

41st day. Polynuclears 81 %; opalescent; jelly clot; yellow; viscid; Esbach 12; organisms intracellular and abundant; endothelials abundant; cells degenerated; specific gravity 1010.

44th day. Polynuclears 90 %; slightly turbid fluid; jelly clot; yellow colour; Esbach 20; specific gravity 1011.5; viscid; organisms intracellular and scanty; cells mixed; endothelials scanty.

Case CVI. Cerebro-spinal fever. Age 45. Duration of illness, 40 days. Recovery.

14th day. Polynuclears 97 %; yellow turbid; coarse clot; Esbach $5\frac{1}{2}$; specific gravity 1008; organisms intracellular and scanty; cells little degenerated; endothelials scanty.

15th day. Polynuclears 87 %; greenish turbid; coarse clot; Esbach $7\frac{1}{2}$; specific gravity 1008; organisms intracellular and scanty; cells degenerated; endothelials abundant.

16th day. Polynuclears 86 %; opalescent; fibrillar clot; greenish; Esbach 6; specific gravity 1009.5; organisms not seen; cells degenerated; endothelials abundant.

17th day. Polynuclears 36 %; opalescent; fibrillar clot; yellow colour; Esbach 13; specific gravity 1012; organisms not seen; cells degenerated; endothelials abundant.

18th day. Polynuclears 26 %; opalescent; jelly clot; straw colour; viscid; Esbach $11\frac{1}{2}$; specific gravity 1011; organisms not seen; cells very degenerated; endothelials scanty.

19th day. Polynuclears 15 %; opalescent; jelly clot; yellow; viscid; Esbach $12\frac{1}{2}$; specific gravity 1010.5; organisms not seen; cells very degenerated; endothelials scanty.

21st day. Polynuclears 10 %; nearly clear; jelly clot; yellow; viscid; Esbach 7; specific gravity 1010; organisms not seen; cells very degenerated; endothelials very abundant.

23rd day. Polynuclears 3 %; nearly clear; jelly clot; yellow; viscid; Esbach $5\frac{1}{2}$; specific gravity 1009; organisms none; cells very degenerated; endothelials scanty.

26th day. Clear; viscid; jelly clot; Esbach 6; specific gravity 1007.5.

29th day. Clear; little viscid; slight jelly clot; Esbach 4; specific gravity 1007.

32nd day. Clear; little viscid; jelly clot; Esbach $2\frac{2}{3}$; specific gravity 1007.75.

36th day. Clear; watery; sparse clot; Esbach $1\frac{1}{2}$; specific gravity 1007.

40th day. Clear; sparse woolly clot; Esbach 1; specific gravity 1007.

Case LXVII. Cerebro-spinal fever. Age 16. Duration of illness, 24 days. Died.

5th day. Polynuclears 92%; yellow turbid; coarse jelly clot; Esbach 13; viscid; organisms intracellular and scanty; cells degenerated; endothelials scanty.

8th day. Polynuclears 92%; yellow turbid; coarse jelly clot; Esbach 9; viscid; organisms scanty; cells degenerated; endothelials scanty.

11th day. Polynuclears 96%; yellow turbid; coarse jelly clot; Esbach 24; organisms scanty; cells degenerated; endothelials scanty; viscid.

14th day. Polynuclears 88%; opalescent; jelly clot; Esbach 10; viscid; yellow colour; organisms scanty; cells degenerated; endothelials abundant.

18th day. Polynuclears 83%; opalescent; jelly clot; Esbach 12; viscid; yellow colour; organisms scanty; cells degenerated; endothelials abundant.

21st day—Polynuclears 85%; opalescent; jelly clot; Esbach 24; viscid; yellow colour; organisms not seen; cells degenerated; endothelials scanty.

Case LXX. Cerebro-spinal fever. Age 25. Duration of illness, 14 days. Died.

5th day. Polynuclears 94%; yellow turbid; coarse clot; Esbach $4\frac{2}{3}$; organisms abundant; cells little degenerated; endothelials scanty.

7th day. Polynuclears 94%; greenish turbid; coarse clot; Esbach 3; organisms intracellular and scanty; cells fresh; endothelials abundant.

9th day. Polynuclears 80%; opalescent; shreddy fibrillar clot; Esbach $3\frac{2}{3}$; organisms intracellular and abundant; cells mixed; endothelials abundant.

13th day. Polynuclears 5%; slightly opalescent; yellow colour; jelly clot; Esbach $10\frac{2}{3}$; organisms not seen; cells degenerated; endothelials scanty.

Case XCIV. Cerebro-spinal fever. Age 48. Duration of illness, 36 days. Died.

8th day. Polynuclears 96%; turbid; coarse clot; Esbach $1\frac{3}{4}$; organisms extra-cellular and scanty; cells degenerated; endothelials scanty.

9th day. Polynuclears 97%; very turbid; coarse clot; Esbach 2; viscid; yellow; organisms extra-cellular and scanty; cells degenerated; endothelials scanty.

34th day. Polynuclears 82%; opalescent; jelly clot; Esbach 9; organisms, extra-cellular scanty, intracellular abundant; cells little degenerated; endothelials abundant; viscid; yellow.

Case CVII. Cerebro-spinal fever. Age $\frac{3}{12}$. Duration of illness, 37 days. Died.

15th day. Polynuclears 58%; opalescent; jelly clot; yellow; viscid; Esbach 7; organisms not seen; cells fairly fresh; endothelials scanty.

16th day. Polynuclears 77%; opalescent; jelly clot; yellow; viscid; Esbach $8\frac{1}{2}$; organisms scanty; cells fairly fresh; endothelials scanty.

19th day. Polynuclears 73%; opalescent; jelly clot; yellow; viscid; Esbach 10; organisms not seen; cells degenerated; endothelials scanty.

23rd day. Polynuclears 70%; opalescent; jelly clot; yellow; viscid; Esbach 12; organisms scanty; cells mixed; endothelials fairly abundant.

26th day. Polynuclears 20%; nearly clear; jelly clot; yellow; viscid; Esbach 14; organisms not seen; cells degenerated; endothelials scanty.

35th day. Polynuclears 25%; nearly clear; jelly clot; yellow; viscid; Esbach 15; organisms not seen; cells degenerated; endothelials scanty.

Case C. Cerebro-spinal fever. Age $\frac{5}{12}$. Duration of illness, 47 days. Died.

12th day. Polynuclears 79%; turbid; coarse clot; yellow; Esbach 50; organisms intracellular and sparse; cells degenerated; endothelials scanty.

13th day. Polynuclears 87%; opalescent; jelly clot; yellow; viscid; Esbach 45; organisms sparse and intracellular; cells degenerated; endothelials scanty.

14th day. Polynuclears 47%; opalescent; jelly clot; yellow; viscid; Esbach 39; organisms not seen; cells very degenerated; endothelials scanty.

16th day. Polynuclears 97%; opalescent; jelly clot; yellow; viscid; Esbach 33; organisms intracellular and abundant; cells fresh; endothelials scanty.

18th day. Polynuclears 78%; opalescent; jelly clot; yellow; viscid; Esbach 32; organisms extra-cellular and abundant; cells mixed; endothelials scanty.

20th day. Polynuclears 80%; opalescent; jelly clot; yellow; viscid; Esbach 30; organisms, extra-cellular abundant, intracellular scanty; cells degenerated; endothelials fairly abundant.

23rd day. Polynuclears 37%; opalescent; jelly clot; yellow; viscid; Esbach 40; organisms extra-cellular and scanty; cells degenerated; endothelials fairly abundant.

26th day. Polynuclears 70%; opalescent; jelly clot; yellow; viscid; Esbach 33; organisms extra-cellular and scanty; cells degenerated; endothelials scanty.

29th day. Polynuclears 54%; opalescent; jelly clot; yellow; viscid; Esbach 36; organisms extra-cellular and scanty; cells degenerated; endothelials fairly abundant.

33rd day. Polynuclears 20%; opalescent; jelly clot; yellow; viscid; Esbach 34; organisms not seen; cells very degenerated; endothelials abundant.

37th day. Polynuclears 30%; opalescent; jelly clot; yellow; viscid; Esbach 36; organisms not seen; cells degenerated; endothelials abundant.

41st day. Polynuclears 28%; opalescent; jelly clot; yellow; viscid; Esbach 27; organisms not seen; cells degenerated; endothelials scanty.

Case XXXVI. Tuberculous meningitis. Age 28. Died.

3rd last day. Polynuclears 2%; clear fluid (nearly); late fine fibrillar clot; organisms fairly abundant; Esbach $5\frac{1}{2}$; specific gravity 1007.75.

2nd last day. Polynuclears 10%; nearly clear fluid; fibrillar clot; organisms fairly abundant; Esbach $8\frac{1}{2}$; specific gravity 1008.5.

Last day. Polynuclears 10%; yellow, nearly clear, viscid fluid; jelly clot; Esbach 8; specific gravity 1008.75.

Case XLV. Tuberculous meningitis. Age 34. Died.

7th last day. Polynuclears 2%; amber-yellow, nearly clear, viscid fluid; jelly clot; Esbach 25; organisms, none.

5th last day. Polynuclears 5%; amber-yellow, nearly clear, viscid fluid; Esbach 20; jelly clot; organisms, none.

2nd last day. Polynuclears 15%; fluid and clot similar; Esbach 10; organisms, none.

Case XXV. Tuberculous meningitis. Age 4 years.

2nd last day. Polynuclears, sparse; slight opalescent fluid; fine fibrillar clot; Esbach 3; organisms, none.

Last day. Polynuclears 9%; opalescent (slightly); yellow; viscid; Esbach 14; organisms, none; jelly clot.

The Specific Gravity.

The estimation of the specific gravity is not of great practical importance. In the majority of cases there is little alteration during the course of the disease, and such variations as do occur are coincident with other conditions in the cerebro-spinal fluid which are more readily ascertained. Individual observers give different estimations, but the normal range appears to be between 1004 and 1007. The presence of turbidity raises the figure as high as 1008 or 1009, and as the matters in suspension become less numerous, the specific gravity falls. A high percentage of albumin also raises the figure. The viscid fluid previously referred to as occurring in certain acute types of meningitis was found to possess the highest specific gravity. In one such case it was estimated as 1012. In numerous samples of turbid fluid a reading was taken both before and after they had been centrifugalized, and in each case the specific gravity was lower in the latter. Where two samples of fluid had been collected at the one puncture, the figure was uniformly higher in the first sample than in the second. The difference, however, was never more than five per 10,000. Tables are appended showing the relationship of the turbidity and the amount of albumin to the specific gravity in some of the cases. These are examples from 341 observations. From these tables it will be seen that although there are marked differences between the individual cases, there is little variation in the specific gravity between the different samples of fluid from the one case during the whole course of the disease, except in the acute haemorrhagic type, of which Mrs. S. (Case CVI) is an example. The chronic cases, on the other hand, show a practically uniform specific gravity (Table IV).

TABLE IV.—Showing the degree of turbidity, the amount of albumin, and the specific gravity on each day of illness, in six cases.

Day of Illness.	Degree of Turbidity.	Albumin in Grammes per litre.	Specific Gravity.
74th	Nearly clear	One	1006.5
75th	"	Seven-eighths	1006.75
76th	"	Three-fourths	1006.5
77th	"	One-half	1006.5
78th	"	One-half	1006.5
79th	"	One-half	1007
80th	"	Three-fourths	1006.5
81st	"	One-half	1007
82nd	"	Three-fourths	1006.75
83rd	"	One	1006.5
84th	"	One	1007
86th	"	Two-thirds	1006.5
89th	"	One	1006.75
93rd	"	One-half	1007
103rd	"	One-half	1006.75
106th	"	Three-fourths	1007
108th	"	One	1006.75
111th	"	One-half	1007
116th	"	One-half	1006.25
122nd	"	One-third	1006.5

Case CXII.—Chronic stage of cerebro-spinal fever. Recovery.

Day of Illness.	Degree of Turbidity.	Albumin in Grammes per litre.	Specific Gravity.
14th	Turbid	5	1008
15th	Slightly turbid	7½	1008.25
16th	Opalescent	9	1009.5
17th	"	13	1012
18th	Slightly opalescent	11½	1011
19th	"	12½	1010.5
21st	"	7	1010
23rd	Nearly clear	5½	1009
26th	"	6	1007.75
29th	"	4	1007
32nd	"	2½	1007.75
36th	"	1½	1007
40th	Clear	1	1007

Case CVI.—Acute haemorrhagic type of cerebro-spinal fever. Recovery.

Day of Illness.	Degree of Turbidity.	Albumin in Grammes per litre.	Specific Gravity.
8th	{ Turbid 1	6	1008
	{ " 2	3½	1007.75
9th	{ " 1	5	1008
	{ " 2	4½	1008
	{ " 1	5½	1008
10th	{ " 2	4½	1007.5
	{ " 3	3½	1007.5

Case XC.—Meningitis (mixed infection), rapid course. Death.

Day of Illness.	Degree of Turbidity.	Albumin in Grammes per litre.	Specific Gravity.
11th last	Nearly clear	¾	1006.75
10th "	"	1	1006.25
9th "	"	¾	1006.5
8th "	"	1½	1006.25
7th "	"	¾	1006.25
6th "	"	1	1006.25
5th "	"	1	1006.5
4th "	"	1½	1006
3rd "	Slightly opalescent	1	1007.25
Last	"	1	1007

Case XL.—Tuberculous meningitis.

Day of Illness.	Degree of Turbidity.	Albumin in Grammes per litre.	Specific Gravity.
6th last	Nearly clear	2½	1007
5th "	"	3	1007
4th "	"	2½	1007
3rd "	Slightly opalescent	2½	1006.75
2nd "	"	3½	1006
Last	"	5½	1009

Case XLIV.—Tuberculous meningitis.

TABLE IV (*continued*)

Day of Illness.	Degree of Turbidity.	Albumin in Grammes per litre.	Specific Gravity.
3rd last	Nearly clear	5½	1007.75
2nd „	„	8½	1008.5
Last	„	8	1008.75

Case XXXVI.—Tuberculous meningitis. Acute haemorrhagic type.

The Coagulum.

No coagulum forms in the normal cerebro-spinal fluid, but the presence of a small quantity of blood resulting from trauma during the puncture may cause a fine clot formation. The presence of fibrin-forming elements, apart from accidental admixture with blood, is always associated with meningeal inflammation. The amount and the character of the clot depend on the degree of turbidity, and they are also, to some extent, related to the amount of albumin in the fluid. The coagulum in a very turbid fluid forms early, usually within five to fifteen minutes from the time of withdrawal. Under such circumstances it is abundant and coarse in character, resembling a dusty cobweb in its appearance (Plate 3, Fig. IV). In an opalescent fluid the clot is later in forming, from half an hour to an hour as a rule, and it is less abundant. The upper layers of the fluid may be nearly clear before the clot is formed. It is composed of a more or less delicate fibrillar network, the fibrillae interlacing in a strikingly fine and regular fashion (Plate 3, Figs. I and II). A fluid which is nearly clear gives a very scanty clot, often invisible, until the fluid is shaken up. It has the appearance in such cases of small particles of cotton-wool suspended in the fluid (Plate 3, Fig. III). These three, the coarse cobweb, the delicate fibrillar, and the fine cotton-wool, are the main types, and between each are varieties modified according to the degree of turbidity and the stage of the disease.

The formation of a coagulum begins in all cases at the surface of the fluid and spreads downwards. When newly formed, the clot is suspended from the centre of surface of the fluid, in the shape of a cone in some cases. In other cases it hangs by a thin thread. If the tube be kept perfectly still, it remains suspended by the surface tension and by its adhesion to the sides of the tube until the inclusion of a large number of cellular elements in its meshes causes it to break away and sink to the bottom. The characters of the clot in each patient, on each day of illness, have been tabulated, and these can be compared with the turbidity (Table VII). It will be seen that during the first four days of illness the coagulum is of the coarse cobweb type. Thereafter the coarseness tends to disappear up to the ninth day, when the clot has more of a shreddy or coarse fibrillar appearance. Towards the end of the fourth week the commonest form is a fine fibrillar coagulum. Clot formation occurs in the fluid at a very early stage of the disease, as soon as the slightest opalescence is noticed, and

although its characters are dependent on the amount of turbidity, it persists for a varying period after the fluid has become practically clear. The fine scanty cotton-wool coagulum was found to be the last pathological sign in the cerebro-spinal fluid. It is very apt to escape observation unless the fluid be well shaken up. In one case (V. M., aged 2 years), which ultimately recovered, a coagulum formed in the fluid on the 280th day of the disease. It is interesting to note in this connexion that Kernig's sign persisted as long as there was clotting, and was the last clinical sign to disappear.

Two varieties of clot, which are not included in the three main types, remain to be described. The first occurs occasionally in moderately acute cases, or in chronic cases where turbidity has been long continued. Innumerable minute shreds of fibrin form under these circumstances, and adhere to the sides and bottom of the tube. These shreds do not unite to form a mass, but remain separate. The presence of this variety apparently indicates a mild inflammatory condition. The second variety, on the other hand, always accompanies a very acute form of meningitis, in which the fluid is of the viscid nature previously described. The clotting occurs very rapidly, in fact almost immediately, and practically the whole fluid coagulates into a jelly-like mass which contracts slowly, like a blood clot.

A close relation was found to exist between the turbidity, the clot, and the pyrexia in the different types of cerebro-spinal fever. The cobweb clot, however, which is associated with a very turbid fluid, tends to become less coarse before there is much obvious difference in the degree of turbidity, and in the later stages, when a turbid appearance has persisted for a long period, the clot may become more or less finely fibrillar. In those cases where the fluid was collected in two or more portions, a difference between the characters of the clot in the first and second samples was observed in fourteen out of the total thirty-six cases. The coagulum in the second portion was finer in nature and less in amount on twenty occasions in these fourteen cases, and this occurrence is apparently the rule. In only one instance (Case XXXIV (p. 162), already quoted in the section on the Turbidity) was the clot in the second portion the more abundant. The second portion showed the lesser amount of clot in this case up to the fifteenth day. On the eighteenth and twentieth days of the illness, the coagulum in the second tube was the more abundant. The patient died on the twenty-seventh day of illness with a vertical extension of the meningitis. It is suggested that the greater amount of clot in the second sample, in conjunction with other signs, indicated extension to the upper part of the cerebro-spinal system.

The appearances of the clot in tuberculous fluids do not show the same wide variation as in cerebro-spinal fever. A coarse clot of the cobweb type never occurs, and the cotton-wool variety is the most common. A very fine fibrillar coagulum is usually associated with the slightly opalescent fluids. The jelly-like clot was present in the three cases where the fluid was of the peculiar viscid nature already described.

The coagulum at all the stages of cerebro-spinal fever was much softer and was more easily broken down than in the tuberculous variety. This difference was obvious when smears were made from the clot. It was almost impossible to spread out the clot from a tuberculous case to make films; the more it was worked with the more stringy it became, whereas the coagulum from an acute pyogenic case was easily broken down to make good films. Percheron attaches great importance to the character of the coagulum. In tuberculous meningitis, he states that it floats in the middle of the fluid, is translucent and of extreme tenuity, and difficult to spread on a slide. If not tuberculous, the coagulum is composed of a rich network, enclosing cellular elements and micro-organisms; in these circumstances it is tenacious, adhering to the sides of the vessel, but spreads out easily.

The Sediment.

A sediment only occurs in a very turbid fluid. It consists of flocculent masses of pus, shreds of fibrin, and various cellular elements. A yellow turbid fluid, half an hour after collection, presents the appearance of an abundant sediment, above which hangs a coarse cobweb clot entangling the finer suspended matters. Clotting always begins in a moderately turbid or opalescent fluid before sedimentation has taken place, and the mass of clot which falls to the bottom after the fluid has been allowed to stand for some time must not be mistaken for a deposit. The presence of sediment is evidence of an extensive purulent exudation of recent origin on the spinal cord. It never occurs after organization has begun. This was the uniform finding post mortem.

The greatest amount of sediment occurred in Case IV, in which it reached half-way up the column of fluid in the test-tube. The deposit is rarely seen after the first week of illness, as by this time the exudate has either become organized or is becoming more widely distributed, so that only thick pus is got by lumbar puncture. A sediment was never observed in the fluid from tuberculous meningitis.

The Reaction.

Normal cerebro-spinal fluid is markedly alkaline, and this reaction was found to be maintained in all the cases included in this series. The degree of alkalinity, however, varies according to the nature and the stage of the meningitis. No exact estimations were made in terms of a known alkali. The method adopted was to add approximately the same amount of phenolphthalein to each specimen of fluid, and to judge the degree of alkalinity by the depth of the red tint produced in the sample. The least degree of alkalinity was evidenced by a faint pinkish opalescence and the greatest degree by a clear red colour. By this means it was found that normal cerebro-spinal fluid possesses the highest, and the turbid fluid in the early stages of acute pyogenic meningitis the lowest, degree of alkalinity. As regards its reaction, the fluid from tuberculous meningitis comes between these limits.

The marked decrease in the alkalinity of the turbid fluids was investigated, and the following facts were observed. The lessened alkalinity was found to coincide with a disappearance of the dextrose which is normally present in cerebro-spinal fluid. Boiling a turbid fluid with Fehling's solution invariably failed to reduce the copper salt. This absence of the sugar was further associated with the presence of lactates in the fluid, as tested by Uffelmann's reagent. The meningococcus of Weichselbaum is known to be an acid-forming organism, and it is presumed that the diplococci break up the dextrose in the fluid, and that the lactic acid, which results from the splitting up of the sugar, neutralizes to a greater or less extent the normal alkalinity of the fluid. In view of the acid-forming properties of the organisms, it is remarkable that not even in those cases where the meningococci were most abundant was the fluid found to be acid. Several samples of fluid, tested within a few hours of the death of the patient, were also faintly alkaline. The foregoing statements only refer to the reaction in the primary acute stage of cerebro-spinal fever. In the late chronic stages, on the other hand, when pyrexia has continued over many weeks and the fluid has remained more or less opalescent, the alkalinity was found to approach more nearly to the normal, even in the presence of living meningococci. This occurrence was proved, in a further series of experiments, to depend on a change in the character of the organism itself. The increase of alkalinity was found to be associated with the reappearance of dextrose in the fluid, and with a decided diminution in the amount of lactates. That the organism had lost its power of breaking up sugar and liberating an acid was shown by cultivations on Loeffler's serum made up with dextrose or glucose, with the addition of neutral-red. An active growth, from the inoculation of this medium with organisms isolated at the acute stages of cerebro-spinal fever, invariably caused a bluish purple colour along the tract of growth; whereas the organism recovered at the chronic stages left the colour of the medium unaltered. Under these circumstances the apparently anomalous condition was sometimes seen, in which fluid from a convalescent acute case possessed a lesser degree of alkalinity than the fluid from a patient in the late chronic stages of the disease, who was seriously ill.

The reaction of the fluid from cases of tuberculous meningitis was also found to be uniformly alkaline. The alkalinity was estimated to be distinctly less than normal but greater than in acute pyogenic infections, and it was constantly associated with the presence of lactates, and also with a decreased amount or an entire absence of dextrose.

The Albumin.

The amount of albumin was estimated throughout the series by means of Esbach's method. A sufficient amount of fluid can be obtained in most cases to fill the tube up to the U mark. All observers agree that albumin is absent from the normal cerebro-spinal fluid, although a proteid substance of the nature of a globulin is present in minute quantities. The presence of albumin can thus be

taken as evidence of meningeal inflammation. The amount varies in a definite manner, according to the nature and the degree of the inflammation. During the first day of illness, in three cases, the estimations were respectively $\frac{1}{4}$, $1\frac{1}{4}$, and $\frac{1}{2}$ grammes per litre. In two cases examined at the end of the first day the amounts were $1\frac{1}{2}$ grammes in one and 9 grammes in the other. The average of seventeen specimens estimated on the second day of illness was $2\frac{3}{4}$ grammes per litre, the highest being $5\frac{1}{2}$ and the lowest $\frac{1}{2}$. The average for the third day was found to be 3 in seventeen cases, the highest reading being $7\frac{1}{2}$ and the lowest $\frac{3}{4}$. The exact estimations in each case will be seen from Table VII, in which the amounts are arranged under each day of illness.

In general, it may be said that a low percentage of albumin in the earlier stages of cerebro-spinal fever is significant of a comparatively mild affection, and a steadily decreasing amount is indicative of a favourable termination. The decrease of the albumin usually accompanies a diminution in the turbidity, a lessening in the amount of coagulum, and a fall in the temperature.

A great majority of the fluids show a smaller amount of albumin at the second and succeeding punctures than at the first. This is probably due to the dilution of the fluid resulting from the increased secretion necessary to re-establish the intracranial pressure after the first puncture. When, on the other hand, the percentage of albumin is greater in the succeeding samples of fluid, this is to be taken as a sign of a progressive inflammation with a grave prognosis. The fluid in the acute stages of cerebro-spinal fever is characterized by a large amount of albumin which is subject to fluctuations, but in the chronic stages the quantity is less and does not vary to the same extent. In the protracted chronic cases, however, the percentage of albumin may steadily increase as the disease continues, and may amount to 4 or 6 grammes per litre. This occurrence is taken to indicate a persistence of the exudate, and it is usually associated with the presence of hydrocephalus. Death usually results in these instances. Case CXI is illustrative. The amount of albumin rose from 2 grammes per litre in the fourth month of illness to 3 grammes in the fifth month, and reached 6 grammes in the sixth month.

The highest amount of albumin is found in those cases of an acute haemorrhagic nature with the viscid fluid already described. The reading in one of these cases (Case C) was 50 grammes per litre on the twelfth day of illness, and at succeeding punctures, eleven in all, the amount never fell below 27 grammes. A consistently smaller amount was found in the second sample, in the cases where the fluid was collected in two portions. Table V gives the figures in each case. The greatest difference observed was 3 grammes per litre in Case XC; where, on the eighth day of illness, the amount was 6 grammes per litre in the first sample and 3 grammes in the second. In the other cases the difference seldom was more than $\frac{1}{2}$ or 1 gramme per litre.

The fluids from cases of tuberculous meningitis do not show the same wide variations as occur in the acute pyogenic infections. Apart from the acute haemorrhagic type of inflammation, the readings are low, and the average lies

between 1 and 2 grammes per litre. The exact figures for each case will be seen in Table IX. The highest reading in an ordinary case was $5\frac{1}{2}$ grammes on the last day of illness, and the same amount occurred in another case on the second last day of illness. The lowest reading was half a gramme per litre in one case on the seventh last day of illness. A lesser amount of albumin was uniformly

TABLE V.—Showing lesser amount of albumin in the second portion of the fluid than in the first. (Esbach units.)

Cerebro-spinal Fever Cases.

Case CVI	32nd day	$2\frac{3}{4}$	$2\frac{1}{2}$		Case LXI	13th day	$\frac{4}{8}$	$\frac{4}{8}$
Case XC	8th "	6	3			19th "	$1\frac{1}{2}$	1
	9th "	5	$4\frac{1}{2}$			23rd "	$1\frac{1}{2}$	$1\frac{1}{2}$
	10th "	$5\frac{1}{2}$	$4\frac{1}{2}$	$3\frac{1}{2}$		30th "	2	$1\frac{1}{2}$
Case IX	65th "	$2\frac{1}{2}$	$1\frac{1}{2}$			40th "	2	$1\frac{1}{2}$
Case LXXXVI	8th "	1	$\frac{1}{2}$			45th "	$2\frac{1}{2}$	2
	14th "	1	$\frac{1}{2}$		Case XIX	2nd "	$1\frac{1}{2}$	$1\frac{1}{2}$
	16th "	1	$\frac{1}{2}$			4th "	$\frac{1}{2}$	$\frac{1}{2}$
Case LXVIII	13th "	$\frac{1}{2}$	$\frac{1}{2}$		Case LXIV	5th "	1	$\frac{1}{2}$
Case XXIII	9th "	$3\frac{1}{2}$	$2\frac{1}{2}$			26th "	$1\frac{1}{2}$	1
Case LXXX	73rd "	$2\frac{3}{4}$	2	$1\frac{1}{3}$		67th "	$1\frac{1}{2}$	$1\frac{1}{2}$
	78th "	$2\frac{1}{2}$	2			69th "	2	$1\frac{1}{2}$
Case LVII	65th "	1	$\frac{1}{2}$			71st "	$2\frac{1}{2}$	$1\frac{1}{2}$
	90th "	$\frac{1}{2}$	$\frac{1}{2}$			87th "	$1\frac{1}{2}$	1
Case LXXI	12th "	$2\frac{3}{4}$	2			102nd "	1	$\frac{3}{4}$
	15th "	$2\frac{3}{4}$	2		Case XLVII	4th "	1	1
	18th "	$2\frac{1}{2}$	2			14th "	$1\frac{1}{2}$	$1\frac{1}{2}$
	21st "	$1\frac{1}{2}$	$1\frac{1}{2}$			19th "	2	$1\frac{1}{2}$
	27th "	2	$1\frac{1}{2}$		Case CXII	31st "	$2\frac{1}{2}$	2
	30th "	1	$1\frac{1}{2}$			39th "	3	$2\frac{1}{2}$
	34th "	2	$1\frac{1}{2}$			99th "	$\frac{1}{2}$	$\frac{1}{2}$
	37th "	3	2		Case CXI	86th "	$2\frac{1}{2}$	2
	42nd "	5	2			93rd "	3	$2\frac{1}{2}$
	47th "	3	$2\frac{1}{2}$			110th "	3	$3\frac{1}{2}$
Case XLI	55th "	$1\frac{1}{2}$	$\frac{1}{2}$			131st "	$4\frac{1}{2}$	$4\frac{1}{2}$
Case LXXXVII	61st "	2	$1\frac{1}{2}$		Case CXII	31st "	$1\frac{1}{2}$	1
Case CIX	7th "	$4\frac{3}{4}$	$4\frac{1}{2}$			53rd "	$1\frac{1}{2}$	$1\frac{1}{2}$
	15th "	$1\frac{1}{2}$	$1\frac{1}{2}$					
	26th "	$1\frac{1}{2}$	$1\frac{1}{2}$					

Tuberculous Cases.

Case XL	Last	1	1		Case XVI	3rd last	3	$1\frac{1}{2}$
	8th "	1	$\frac{1}{2}$	$\frac{1}{2}$	Case XIV	7th "	$3\frac{1}{2}$	$2\frac{1}{2}$
	9th "	$1\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{2}$		10th "	$1\frac{1}{2}$	$1\frac{1}{2}$
	10th "	1	$\frac{1}{2}$	$\frac{1}{2}$		13th "	2	$1\frac{1}{2}$
Case L	2nd "	1	1		Case XXVI	3rd "	$2\frac{1}{2}$	$1\frac{1}{2}$
Case XXV	2nd "	3	$1\frac{1}{2}$		Case IX	4th "	$1\frac{1}{2}$	1
Case XXXIX	5th "	$1\frac{1}{2}$	1			6th "	1	$1\frac{1}{2}$
Case XXXIV	8th "	1	$\frac{3}{4}$	$\frac{1}{2}$	Case VII	9th "	$1\frac{1}{2}$	1
Case VIII	4th "	3	$\frac{3}{4}$	$\frac{1}{2}$		14th "	1	$\frac{3}{4}$
Case XLIV	4th "	$2\frac{1}{2}$	$1\frac{1}{2}$					
	5th "	3	2					

found in the second sample, in those cases where the fluid was collected in two portions. Of the three acute cases (XXXVI, XXV, and XLV) in which the fluid was of the viscid nature already alluded to, the highest amount of albumin was 25 grammes per litre in one case, on the seventh last day of illness. The lowest was 3 grammes in another case, on the second last day. The variations

in the amount of albumin in the tuberculous cases were numerous, and were found to be without obvious significance. In some of the cases the amount increased towards the day of death, and in others it remained practically constant throughout the course of the illness. In other cases, again, a fall was observed as the disease progressed.

Rous found in nine cases (seventeen punctures) that the average 'protein content' did not measure more than 1 gramme, the highest being 10 grammes and the lowest $\frac{3}{4}$ of a gramme per litre. He states that, in the one case where he found albumin to the extent of 10 grammes per litre, at the post mortem 'an extraordinary gelatinous meningitis' was found. It may be that this case was similar to the ten cases which have been particularly described in the section on the consistence of the fluid (q.v.). Four of these cases came to post mortem, three of cerebro-spinal fever and one of tuberculous meningitis. The above condition, however, was not observed in any of them. Macroscopically they presented appearances similar to those found in the ordinary types of meningitis.

The Sugar.

The presence of a sugar in the form of galactose has been definitely proved by numerous observers. Its absence is a certain sign of meningitis, but it is not equally true to say that it is never present in meningitis. Every sample of fluid from each case included in this paper was tested by boiling with Fehling's solution. The results prove that sugar is absent from the fluid during the acute stages of cerebro-spinal fever. This finding was invariable, and it depended, as previously shown, on the presence of active acid-forming meningococci. Fehling's solution is more or less actively reduced by the cerebro-spinal fluid, in every case as soon as the organism dies out, and this test forms the readiest means of ascertaining the progress of the cases in actual practice. A reduction of Fehling's solution, in association with a negative result on cultivation of the fluid, must however be interpreted with caution in the later stages of epidemic cerebro-spinal meningitis. Difficulty is frequently met with in cultivating the organism at this stage of the disease, and, in addition, sugar may be present in association with living meningococci. This occurrence has already been shown to depend on the fact that the organism may lose its power of breaking up sugar in the later periods of its existence. The reduction of the copper salt, nevertheless, is a reliable test in those stages before chronicity has become well established, and the absence of pyrexia is an additional proof of the cessation of the infective process. Even while the fluid was still slightly opalescent with abundant fibrillar coagulum, the absence of sugar in many cases was found to be the first sign of a favourable termination of the disease.

In five cases of a chronic nature sugar was present in the fluid at some periods and absent at others. In the former instances the cultures were negative, and in the latter, positive. This occurrence goes to prove that the organisms may remain localized or quiescent for a time, and may become active again under

suitable conditions. In these cases, however, the temperature is as a rule unsettled, and consequently it would be unwise to assume that the presence of sugar indicates a favourable prognosis. Table VI shows the changes in two of the five cases quoted.

TABLE VI.—Showing conditions associated with a reduction or non-reduction of Fehling's solution by boiling it with the fluid from cases of cerebro-spinal fever in the chronic stage. Cultures positive when Fehling unreduced, and negative when reduced.

Case LXXI.

Day.	Polynuclears.	Esbach.			
27th	66 %	2	Opalescent	Fehling	not reduced
30th	58 %	1 $\frac{3}{4}$	"	"	reduced
34th	61 %	2	"	"	not reduced
37th	57 %	3	"	"	reduced
42nd	63 %	5	"	"	not reduced
47th	69 %	3	"	"	not reduced

Case CXI.

Day.	Polynuclears.	Esbach.			
139th	77 %	4 $\frac{3}{4}$	Opalescent	Fehling	not reduced
147th	87 %	6	"	"	reduced
153rd	82 %	4 $\frac{3}{4}$	"	"	not reduced
164th	81 %	3	"	"	reduced
178th	76 %	2 $\frac{1}{2}$	"	"	reduced
180th	88 %	3	"	"	not reduced

In tuberculous meningitis, sugar was found to be present in the great majority of the cases, and at all stages of the disease; 122 specimens were examined. An active reduction on boiling of the Fehling's solution occurred in fifteen, a partial but decided reduction in 102, and no reduction at all in only four instances. Complete absence of sugar was observed in only two cases. It was noted in the last week of illness, three times in one case and once in the other, and in each case at other times, there was a slight reduction of Fehling's solution. Fürbringer states that he found sugar present only as an exception in cases of tuberculous meningitis.

Urea, Phosphates, Lactates, and Choline.

An extended series of quantitative estimations of these substances in cerebro-spinal fluid does not come within the scope of the present work, but a certain number of observations have been made, and these will be briefly described.

Urea.—According to Hammarsten, 'Urea occurs in the cerebro-spinal fluid, but not always.' Twenty-five cases of this series have been examined, and the quantity of urea ascertained by means of Southall's ureometer. In twenty-three only a trace was found, but in the other two the amount was definite. In the fluid taken immediately after death, in a chronic case, the quantity found was 0.5 per cent., and in the second case, which was acute, the fluid obtained on the day before death contained $\frac{1}{10}$ per cent. Nothing of any clinical importance was noted during these observations.

Phosphates.—Fifty-six specimens of fluid from fifteen cases were examined for the presence of phosphates. In all the samples, whether qualitatively or quantitatively estimated, phosphates were found abundantly. The exact significance of these in pathological conditions was not determined, as the amount in normal cerebro-spinal fluid is not known. In twelve instances a quantitative analysis was made by means of uranium nitrate. The variations in the amounts present in the different cases were not great, ranging only, when measured as P_2O_5 , from 3 per cent. to 5 per cent. The precipitate observed in a qualitative examination of these twelve samples resembled very closely that obtained in the remaining thirty-eight specimens, so that they may be taken as an indication of what commonly exists in meningitis. There was little or no difference to be observed between the samples taken from the acute and chronic cases of cerebro-spinal fever and of tuberculous meningitis.

Lactates.—The presence of lactates, as tested by Uffelmann's reagent, has already been alluded to. The highest amounts are found in the early stages of cerebro-spinal fever when the fluid is turbid and the organisms active. The quantity is diminished when the inflammatory process is subsiding and the organisms have died out. The disappearance of the lactates in these cases is associated with the reappearance of sugar in the fluid. In the late chronic stages of cerebro-spinal fever, however, when the organism has lost its power of breaking up the dextrose, lactates are not formed to any appreciable extent. In the tuberculous cases, lactates were uniformly present in the fluid in association with a reduced quantity or complete absence of sugar.

Choline.—Tests for choline were carried out in twenty-five specimens of fluid, twenty from acute pyogenic and five from tuberculous meningitis. This substance was found in each instance. The method employed for its detection was that suggested by Mott and Halliburton. Absolute alcohol is added to the fluid, and the precipitate which forms is filtered off. The filtrate is then evaporated to dryness with moderate heat, and the residue taken up with absolute alcohol. This process is repeated several times with the object of removing the proteid and the salts of potassium and ammonium. The final residue is taken up with 15 per cent. alcohol, and an alcoholic solution of platinum chloride added. On evaporating this solution to dryness at $40^{\circ}C$., yellow octahedral crystals of choline platino-chloride are seen. The alloxan test, suggested by Rosenheim, was employed to confirm these results. In this test, a few drops of a concentrated solution of potassium chloride are added to a concentrated solution of the platino-chloride of choline. The heavy precipitate of potassium platino-chloride which forms is filtered off. The filtrate, on evaporating in a white porcelain basin, after the addition of a saturated solution of alloxan, gives a rose-violet colour. This colour changes to a deep blue violet on the addition of an alkali, and is discharged altogether by mineral acids. The exact significance of the presence of choline in the fluid from the various types of meningitis was not accurately determined. Mott and Halliburton regard it as evidence of the destruction of nerve tissue. In minute quantities, choline is a

normal constituent of the cerebro-spinal fluid, but means were not available to determine whether the amount present in the cases of meningitis was much or little in excess of the normal. Rosenheim states that he was unable to find choline in the fluid from a single case of posterior basic meningitis which he examined. Donath, however, found choline present in several cases of meningitis. He used the polariscope in the detection of the crystals.

The Cytology.

The cytology of the cerebro-spinal fluid has now been worked at by many observers, and they are mainly agreed that the only cell-elements present in normal conditions are the small and large mononuclear leucocytes. The source of these, however, is still in dispute, but it is probable that many of them are of endothelial origin. The number of these cells is increased in many chronic diseases of the spinal cord, such as tabes, and in these cases it is considered—more especially by the French observers—important accurately to estimate the number per cubic mm., from the point of view of diagnosis. In all forms of meningitis, however, the difference from the normal is so marked that this procedure is unnecessary, even were it uniformly accurate.

The fluids from a large number of cases, other than those of meningeal inflammation, have been examined during the course of the present investigations. Cases of scarlet fever, enteric fever, whooping-cough, erysipelas, cerebral tumour, epilepsy, tetany, acute lobar pneumonia, acute broncho-pneumonia, gastro-enteritis, uraemic coma, and various minor ailments were punctured. The centrifugalized sediment in each instance was found to contain very few cells, a single cell being seen in one out of two or three fields of the microscope. The majority of cells in these cases were definitely lymphocytes, and endothelial cells were only occasionally seen. Even apart from the presence of opalescence or of coagulum—for instance, at an early stage of tuberculous meningitis or at a late stage of cerebro-spinal fever—the cellular elements are so obviously in excess of the normal, that the presence of meningitis cannot be overlooked. Generally speaking, a preponderance of polymorphonuclear leucocytes betokens a pyogenic infection, and a mononuclear exudate is characteristic of tuberculous meningitis. Other cells of endothelial nature, shed during the course of the inflammation from the pia arachnoid, are found in both varieties of meningitis. As regards the type of cells which act as phagocytes, intracellular organisms were observed inside the polynuclear cells only.

The Polymorphonuclear Leucocytes.

The polynuclear cells are always found in greatest amount, both absolutely and relatively, in cases of pyogenic meningitis. Their presence in large numbers causes a more or less marked turbidity of the fluid. When present in such proportions as to render the fluid turbid, they are always associated with a pyogenic infection, but their significance in a slightly opalescent fluid is less definite, as in

some cases of tuberculous meningitis they are present in large numbers. In view of the fact that the absolute number of the leucocytes is sufficient evidence of meningitis, the percentage estimation of the polynuclear and mononuclear cells comes to be the important procedure as regards the diagnosis between the pyogenic and the tuberculous varieties, and as regards the prognosis of the acute cases.

Differential counts are of value when the question of diagnosis, apart from the presence of organisms, arises between a chronic case of cerebro-spinal fever and an ordinary case of tuberculous meningitis. In the former, a regular and definite increase or decrease in the percentage of polymorphonuclear cells occurs from time to time. These alterations are associated with corresponding changes in the appearance of the fluid, in the coagulum, and in the temperature. In those tuberculous cases, on the other hand, where the cell-content is not entirely mononuclear, the polynuclear percentage alters little, or in an irregular manner. A differential count from day to day, however, is of most value in the prognosis of the acute cases of cerebro-spinal fever. In the early stages of this disease the polynuclear cells are greatly in excess. The percentage has been estimated in each case, and the results will be seen in Table VII arranged under each day of illness.

It will be observed that in one case out of the three examined early on the first day of illness there were no polymorphonuclear cells. The percentage in the other two cases was 75 and 90 respectively. In two cases punctured at the end of the first day, the polymorphs were 87 per cent. in the one case and 88 per cent. in the other. Counts were made in seventeen cases on the second day of illness. The average percentage was 89, the highest being 97 and the lowest 70. Seventeen cases also were examined on the third day, when the greatest number was 99 per cent., the smallest 20 per cent., and the average 88 per cent. The estimations numbered twenty-four on the fourth day of the disease, on which day the numbers ranged between 97 per cent. and 58 per cent., with an average of 89 per cent. From the first to the seventh day the average never fell below 86 per cent., but on the eighth day it fell to 76 per cent. Thereafter, until the twenty-second day, the average percentage fluctuated between 67 and 84. The observations from this day onwards are not sufficiently numerous to allow of fair averages being made.

The first day on which a definite fall in the percentage of polynuclear cells took place was noted as the fourth day in Case XXXIV, where the polymorphs fell from 97 per cent. on the third day to 80 per cent. on the fourth. Case XVI, already alluded to as being atypical, is not here taken into account. By the sixth day five cases have fallen below 80 per cent., one of them showing an entire absence of polynuclear cells (Case XXIV, a mild abortive type). By the eighth day the count is less than 20 per cent. in other two cases. Thereafter an increasing number of falling percentages is observed. A high polymorphonuclear percentage may persist for long periods. In Case CXI the enumeration showed 84 per cent. on the 170th day of illness, and in another case, V. M., aged 3 years (not included in the tables), the polynuclear cells were 87 per cent. on the 281st day of the disease. This patient recovered after an illness which lasted practically a year.

TABLE VII.—Showing the polynuclear percentage, the condition of the cells, the number and position of the organisms, the amount of albumin, the occurrence of endothelial cells, and the character of the coagulum in the fluid from one hundred and twenty cases of cerebro-spinal fever.

P = Polymorphs. D = Degeneration. E = Endothelial. O = Organisms. A = Albumin. C = Coagulum.
 Degeneration column: F = Fresh, L = Little, D = Degenerated, VD = Very degenerated, M = Mixed. Endothelial column: VA = Very abundant, A = Abundant, S = Scanty, VS = Very scanty. Organisms column: I = Intracellular, E = Extra-cellular, A or a = Abundant, S or s = Scanty, VS = Very scanty. Coagulum column: C = Coarse cobweb, F = Fibrillar, W = Woolly, J = Jellylike, SC = Slightly cobweb, SF = Shreddy fibrillar.

Case	P	D	E	O	A	C	Case	P	D	E	O	A	C
During 1st day.							End of 1st day.						
I	75	F	VS	VS	1	F	III	87	LD	A	Es	9	C
II	90	F	VS	VS	1	0	IV	88	F	S	A	1	C
III	0		VS	VS	1	0							
2nd day.							3rd day.						
V	85	D	A	S	4	C	XI	93	D	A	Es	4	C
VI	95	LD	A	Es	2	C	XVI	20	F	A	0	1	SF
VII	83	D	A	0	3	C	XXII	87	MD	A	A	1	C
VIII	95	D	A	S	1	C	XXIII	93	D	S	VA	1	C
IX	93	D	A	S	1	C	XXIV	97	LD	S	VA	7	C
X	96	LD	A	S	2	C	XXV	93	LD	A	Ia	1	C
XI	93	LD	S	S	3	C	XXVI	99	LD	VA	0	1	C
XII	90	D	VA	Es	4	C	XXVII	95	VD	A	Es	1	C
XIII	95	LD	S	Es	2	C	XXVIII	89	LD	A	Is	1	C
XIV	89	F	A	0	2	C	XXIX	77	F	VS	VS	4	C
XV	93	LD	A	VS	5	C	XXX	96	F	A	Es	4	C
XVI	77	F	S	0	1	C	XXXI	88	D	A	S	1	C
XVII	70	LD	VS	0	1	C	XXXII	94	LD	S	VA	5	C
XVIII	90	D	S	0	2	C	XXXIII	94	LD	S	S	3	C
XIX	88	F	S	0	2	C	XXXIV	97	F	A	Is	2	C
XX	96	LD	S	Es	4	C	XXXV	99	F	S	Is	4	C
XXI	97	D	S	Es	2	C	XXXVI	94	F	S	Is	5	C
17	89				2	C	17	88				3	

TABLE VII (continued)

Case	P	D	E	O	A	C	Case	P	D	E	O	A	C	Case	P	D	E	O	A	C
IV	95	LD	A	S	3 ¹	C	VI	96	D	A	S	1 ¹	SC	IX	82	D	A	Ea	1 ¹	SC
XIII	96	D	VA	Ea	2 ¹	C	X	90	D	A	S	1 ¹	SC	XVII	87	LD	S	0	1 ¹	SC
XVI	86	F	A	S	3 ¹	SF	XXI	96	D	S	A	1 ¹	C	XVIII	85	VD	A	Is	1 ¹	SC
XIX	95	LD	S	0	6 ¹	C	XXVIII	91	LD	VS	Is	2	SC	XXIII	94	D	A	Ea	5 ¹	C
XXX	97	F	A	Ea	1	C	XXXIII	71	LD	A	S	4 ¹	C	XXX	99	LD	A	S	1	SC
XXXIV	80	MF	A	0	1	SC	XXX	97	LD	A	Ea	3	C	XXXIII	92	D	S	S	1	SC
XXXV	81	F	A	Is	4	C	XXXII	94	D	A	Ea	3	C	XXXIV	79	D	VA	S	1	SC
XXXVI	97	LD	A	Is	4	C	XXXI	86	LD	VA	Is	1	SC	XXXV	92	MD	VA	Is	1	SC
XXXVII	91	MLD	A	Ea	4	C	XXXIV	95	LD	A	0	3 ¹	C	XXXVI	79	D	D	S	1 ¹	SF
XXXVIII	89	MD	S	S	1	SC	XXXV	89	LD	A	Is	1 ¹	SC	XXXVII	95	D	A	Ea	1 ¹	C
XXXIX	96	LD	S	S	2 ¹	C	XLVI	96	LD	A	Is	4	C	XLVI	95	VD	S	A	1	C
XL	58	LD	A	Ea	2 ¹	C	LIII	80	LD	A	Is	2 ¹	C	LVI	78	D	A	0	3	FW
XLI	90	MD	S	Es	1	C	LIV	93	F	S	Is	2 ¹	C	LX	84	LD	VS	Is	1 ¹	SF
XLII	91	VD	A	Ea	1	SC	LV	96	LD	VA	VS	3	C	LXVI	94	F	A	Ea	1 ¹	C
XLIII	93	MD	VS	A	1 ¹	SC	LVI	87	MD	A	Is	1 ¹	C	LXVII	81	VD	A	S	1	SF
XLIV	96	LD	S	Ea	7	C	LVII	88	MD	A	S	1 ¹	C	LXXVIII	97	VD	A	Is	1	C
XLV	89	D	S	Fa	1 ¹	C	LVIII	96	MD	S	S	2	C	LXXVII	70	D	VS	0	1 ¹	SC
XLVI	95	LD	A	A	2 ¹	C	LIX	84	LD	S	Ea	1 ¹	C	LXXVIII	95	LD	S	S	1	C
XLVII	84	LD	A	Ea	1	C	LX	91	LD	VS	Is	1 ¹	SC	LXXIX	91	LD	S	Ea	1 ¹	C
XLVIII	93	D	S	Ea	5 ¹	C	LXI	99	D	VS	S	1 ¹	C	LXXX	84	MF	A	Is	1 ¹	C
XLIX	95	D	A	Es	2	C	LXII	97	MF	S	Es	1	C	LXXXI	84	MF	A	Is	1 ¹	C
L	93	LD	VS	Is	2	C	LXIII	94	LD	A	0	1	C							
LI	93	LD	A	S	1 ¹	C	LXIV	93	F	VS	Is	1	C							
LII	86	LD	A	S	1 ¹	C	LXV	90	LD	VA	A	3 ¹	C							
							LXVI	96	LD	A	Ea	13	CJ							
							LXVII	92	LD	S	Is	1 ¹	SC							
							LXVIII	94	VD	A	VA	5	C							
							LXIX	97	LD	VS	A	4 ¹	C							
							LXX	94	LD	S	Ea	5 ¹	C							
							LXXI	90	MF	S	Es	4	C							
							LXXII	97	D	A	Is	0	C							
							LXXIII	84	LD	A	Is	4 ¹	C							
							LXXIV	85	F	S	Es	4	C							
							LXXV	92	F	S	Es	0	C							
							LXXVI	89	D	VS	0	3 ¹	SC							
24	89					2 ¹	85	91					2 ¹	20	87					1 ¹
															86					2 ¹

TABLE VII (continued)

Case	P	D	E	O	A	C	Case	P	D	E	O	A	C	Case	P	D	E	O	A	C			
20th day.																							
XXXIV	97	MF	S	Ia	9 $\frac{1}{2}$	SC	IX	77	D	A	0	1 $\frac{1}{2}$	SC	XVII	72	LD	S	0	1 $\frac{1}{2}$	SF			
XXXVI	86	MD	A	0	6	F	XXIII	92	VD	A	Es	7	C	XXXIV	98	LD	S	Is	9 $\frac{1}{2}$	SC			
LXXII	4	VD	VS	S	1 $\frac{1}{2}$	W	XXXVI	77	MD	S	Is	1 $\frac{1}{2}$	J	LXIV	93	D	S	0	1 $\frac{1}{2}$	SF			
LXXXVII	92	F	S	Is	2 $\frac{1}{2}$	FW	LXXII	88	D	S	Is	2 $\frac{1}{2}$	SF	LXVI	34	MD	S	0	1 $\frac{1}{2}$	FW			
LXXXVI	0		S	0	2 $\frac{1}{2}$	FW	LXVII	85	D	S	0	2 $\frac{1}{2}$	J	LXXVIII	44	VD	S	Es	1 $\frac{1}{2}$	F			
XCIII	70	MD	VA	Is	2 $\frac{1}{2}$	SF	LXXI	52	D	VA	S	1 $\frac{1}{2}$	F	LXXXVIII	80	MD	A	Is	1 $\frac{1}{2}$	SC			
XCVIII	74	VD	VS	0	2	FW	LXXXI	15	VD	S	0	1 $\frac{1}{2}$	FW	XCV	97	D	A	Es	1 $\frac{1}{2}$	C			
XCIX	73	LD	VS	Ia	1 $\frac{1}{2}$	SF	LXXXIX	31	VD	S	Ia	1 $\frac{1}{2}$	C	XCVI	54	LD	S	0	1 $\frac{1}{2}$	F			
C	80	D	A	Es	30	J	XC	0	A	0	Is	1 $\frac{1}{2}$	W	XCVII	15	MD	VS	0	1 $\frac{1}{2}$	C			
CV	97	D	S	Es	4 $\frac{1}{2}$	C	XCII	72	VD	A	Is	1 $\frac{1}{2}$	F	CXV	85	D	S	S	2 $\frac{1}{2}$	C			
CXI	83	LD	S	Es	2 $\frac{1}{2}$	SF	CI	72	D	A	0	1 $\frac{1}{2}$	F										
							CIV	99	D	S	VA	0	SC										
							CVI	10	VD	VA	0	7	J										
							CXII	90	LD	A	Is	0	SC										
							CXIII	93	D	A	0	1	SF										
							CXIV	91	MD	S	Is	1 $\frac{1}{2}$	F										
11	75				5 $\frac{1}{2}$		16	73				4		10	67				2 $\frac{1}{2}$	15	59		5 $\frac{1}{2}$
24th day.																							
XXIII	90	VD	A	A	6 $\frac{1}{2}$	C	VII	82	MF	A	Es	2	SC	XXXIV	97	D	S	Es	4 $\frac{1}{2}$	SF			
XXXIV	98	MD	A	Ia	1	C	IX	70	D	A	S	2 $\frac{1}{2}$	F	XXXVI	29	VD	A	0	8 $\frac{1}{2}$	J			
XLIII	94	VD	A	A	1 $\frac{1}{2}$	C	XXVIII	78	MD	A	0	1 $\frac{1}{2}$	FW	LXXII	92	D	A	0	1 $\frac{1}{2}$	SF			
LXII	95	VD	VS	Ia	1 $\frac{1}{2}$	SC	XCVI	81	D	A	Ia	1 $\frac{1}{2}$	FW	XCIII	35	MD	A	0	2 $\frac{1}{2}$	FW			
LXIII	80	LD	S	Is	1 $\frac{1}{2}$	F	XCIII	43	VD	VS	0	3 $\frac{1}{2}$	FW	XCIV	60	VD	S	S	3	SC			
LXXX	90	LD	A	S	1 $\frac{1}{2}$	SF	CXIII	91	D	A	Is	1 $\frac{1}{2}$	SC	CXVII	20	D	VS	0	3	SC			
LXXXVI	0		S	0	2 $\frac{1}{2}$	W	CXVII	89	D	S	Es	1 $\frac{1}{2}$	SC	C	70	D	S	Es	33	J			
XCIX	57	D	A	A	2	FW								CVI	0	VD	VS	0	6	W			
CIV	92	VA	A	A	1 $\frac{1}{2}$	SF								CVII	20	VD	VS	0	14	J			
CXIV	90	LD	A	S	1	F								CIX	0	S	S	0	1 $\frac{1}{2}$	SF			
CXVII	82	VD	VS	0	3	SC								CXII	96	VD	S	Ia	2 $\frac{1}{2}$	SF			
11	86				2		7	76				2		12	60				6 $\frac{1}{2}$	8	84		2
27th day.																							
XXIII	86	VD	A	A	1 $\frac{1}{2}$	C	XXIII	86	VD	A	A	1 $\frac{1}{2}$	C	XXIII	86	VD	A	A	1 $\frac{1}{2}$	C			
XXXIII	93	D	A	S	3	FW	XXXIII	93	D	A	S	3	FW	XXXIII	93	D	A	S	3	FW			
XXXVIII	92	MF	S	Ia	1 $\frac{1}{2}$	SC	LXXII	92	MF	S	Ia	1 $\frac{1}{2}$	SC	LXXII	92	MF	S	Ia	1 $\frac{1}{2}$	SC			
LXXI	66	MD	A	S	2	F	LXXI	66	MD	A	S	2	F	LXXI	66	MD	A	S	2	F			
LXXXVIII	71	D	A	0	1 $\frac{1}{2}$	F	LXXXVIII	71	D	A	0	1 $\frac{1}{2}$	F	LXXXVIII	71	D	A	0	1 $\frac{1}{2}$	F			
CIV	88	VD	VA	A	1 $\frac{1}{2}$	SF	CIV	88	VD	VA	A	1 $\frac{1}{2}$	SF	CIV	88	VD	VA	A	1 $\frac{1}{2}$	SF			
CXIII	90	MD	S	Ia	2 $\frac{1}{2}$	C	CXIII	90	MD	S	Ia	2 $\frac{1}{2}$	C	CXIII	90	MD	S	Ia	2 $\frac{1}{2}$	C			

TABLE VII (continued)

Case	P	D	E	O	A	C	Case	P	D	E	O	A	C	Case	P	D	E	O	A	C
28th day.																				
XVII	74	MF	A	0	1½	F	VII	94	D	VA	S	1½	SC	XXIII	92	LD	A	Ea	S	C
XLI	77	VD	S	A	1	FW	IX	51	D	A	0	2	SF	LXI	88	LD	S	Ea	2	
XLVII	9	D	S	S	1½	FW	LXIII	57	VD	S	0	2	F	LXXI	58	D	A	0	1½	SF
LVII	13	VD	A	0	1½	FW	LXXX	93	D	A	S	1½	SF	XCIX	0	MD	VA	Is	2	
LXXXVII	11	D	S	Es	2	FW	C	54	D	A	Es	36	J	CXI	85	MD	VA	Is	2	
LXXXVIII	75	MD	A	Vs	1½	SF	CVI	0	VA	0	4	J	C							
LXXXIX	93	D	S	0	4	W	CXVIII	89	LD	A	Ea	2	C							
XCIII	3	VD	S	0	4	W														
CXVII	90	MF	VS	0	4½	SC														
9	50				2		7	73				6½		5	80				2	
32nd day.																				
XLI	81	VD	S	Is	7	SF	VII	95	D	VA	Vs	2	SC	IX	48	LD	S	0	3	F
LVII	44	D	A	Is	1	FW	XVII	63	MD	VA	A	1½	F	XXIII	86	D	A	A	0	3
LXXXVIII	75	VD	S	0	2	F	XXXIII	88	MD	A	S	1½	F	LXXI	61	D	A	0	2	C
LXXXVIII	77	VD	A	S	2½	F	XLIII	93	LD	A	Is	2	SC	LXXX	84	VD	A	0	1½	SF
LXXXIX	98	LD	S	Ea	1½	FW	C	20	VD	A	0	34	J	XCII	68	VD	A	0	2½	F
XCVII	70	MF	A	S	2½	SF	CXIII	94	MF	S	Is	3	C	XCIV	82	LD	A	Ea	9	J
CVI	0	VA	0	2½	J	SC	CXVI	91	F	S	Is	3	SF	CXI	78	MF	S	Is	2½	SF
CXVIII	70	D	A	Is	4½	SC														
8	73				2½		7	77				6½		7	72				7	
36th day.																				
XXXVIII	97	MD	VS	Ea	3½	SC	XXIII	86	LD	A	Ea	7	C	VII	95	D	A	A	S	2½
LVII	9	VD	A	S	1	F	LXXI	57	D	A	0	3	F	IX	42	LD	S	S	0	2½
LXXXIX	96	D	S	Ea	2	FW	LXXXVIII	77	MD	A	S	1½	F	XXXIII	68	D	A	0	4½	P
CVI	0	0	0	1½	C		XCIX	0	VA	0	1	FW	XXXVI	25	VD	A	S	A	1	SC
CXIII	88	MD	A	Ea	1½	C	C	30	LD	A	0	36	J	XXI	88	VD	S	A	1	SC
							CXIX	65	LD	S	0	1	SF	LXXX	70	VD	A	Is	2	SF
														LXXXIX	92	MD	VS	S	2	SF
														CXVIII	66	LD	A	Is	3½	SF
5	72				4½		6	63				8½		8	68				3	
31st day.																				
XXXVIII	41	D	A	0	1½	F	XXXVIII	41	D	A	0	1½	F	XXXVIII	41	D	A	0	1½	F
LXII	73	VD	S	0	1	SF	LXII	73	VD	S	0	1	SF	LXII	73	VD	S	0	1	SF
LXIV	91	MD	A	Is	1½	F	LXIV	91	MD	A	Is	1½	F	LXIV	91	MD	A	Is	1½	F
LXXVII	4	D	S	0	1½	W	LXXVII	4	D	S	0	1½	W	LXXVII	4	D	S	0	1½	W
LXXXVIII	0	0	0	3½	SF		LXXXVIII	0	0	0	3½	SF		LXXXVIII	0	0	0	3½	SF	
CIV	89	D	S	Ea	2½	SF	CIV	89	D	S	Ea	2½	SF	CIV	89	D	S	Ea	2½	SF
CXII	83	D	A	Is	3	SF	CXII	83	D	A	Is	3	SF	CXII	83	D	A	Is	3	SF
7	63				2		7	63						7	63				2	
35th day.																				
LXI	60	D	S	Ea	3	SF	LXI	60	D	S	Ea	3	SF	LXI	60	D	S	Ea	3	SF
LXIII	37	D	S	0	2½	FW	LXIII	37	D	S	0	2½	FW	LXIII	37	D	S	0	2½	FW
LXIV	77	D	A	0	1½	SC	LXIV	77	D	A	0	1½	SC	LXIV	77	D	A	0	1½	SC
CIV	95	MF	S	Ea	1½	J	CIV	95	MF	S	Ea	1½	J	CIV	95	MF	S	Ea	1½	J
CVII	25	D	S	0	15	C	CVII	25	D	S	0	15	C	CVII	25	D	S	0	15	C
CXII	88	D	A	Va	3	SF	CXII	88	D	A	Va	3	SF	CXII	88	D	A	Va	3	SF
CXVII	89	MF	A	A	6	C	CXVII	89	MF	A	A	6	C	CXVII	89	MF	A	A	6	C
CXVIII	69	D	A	Is	5½	C	CXVIII	69	D	A	Is	5½	C	CXVIII	69	D	A	Is	5½	C
8	67				4½		8	67						8	67				4½	
39th day.																				
XLIII	20	VD	A	0	3½	SF	XLIII	20	VD	A	0	3½	SF	XLIII	20	VD	A	0	3½	SF
CXVI	95	MF	S	Is	4	SF	CXVI	95	MF	S	Is	4	SF	CXVI	95	MF	S	Is	4	SF

It has already been shown that there is a close relation between the alterations in turbidity, the coagulum, and the pyrexia at the different stages of cerebro-spinal fever. The changes in the number of the polynuclear cells are similarly related to these. A decreasing turbidity, a lessening clot, and a falling temperature are usually associated with a diminishing number of polymorphs, and a recrudescence in the one condition is accompanied by a corresponding change in the others. The alterations, however, were not exactly synchronous or equal in degree in all the cases. The temperature in the cases which end in cure by crisis is usually normal for a day or two before the polymorphonuclear cells entirely disappear from the fluid, and in the chronic cases where remissions occur, a return of the pyrexia usually precedes an increase in the polymorphs.

A fall in the polynuclear percentage is also found to precede, or at least to be more obvious than, a clearing up of the fluid in some cases. In the chronic cases the degree of opalescence is found to be a less reliable guide than the enumeration of the cells. Quite frequently, at such times, fluids from different cases which present very similar appearances show marked differences in the differential counts. A fluid which contains 40 per cent. of polynuclear cells may be more decidedly opalescent than one which has a percentage of 70. In explanation of this occurrence, it has been observed that a decreasing percentage of polymorphs is not entirely due to the disappearance of these cells. An actual as well as a relative increase in the number of mononuclears takes place, so that the total number of cells of both kinds causes a decided opalescence, although the proportion of polymorphonuclear cells is small. The coagulum also is found to persist for a varying period after the cells have become mononuclear.

It is noteworthy that only on three occasions in over 1,000 estimations was the polynuclear percentage more than 99. This high percentage was found in Case LXII on the twelfth day of illness, in Case CV on the eighteenth day, and in Case CIV on the seventy-fourth day. The first case recovered, and the other two died. In those cases where the fluid was collected in separate portions, differential counts were made from each specimen. When a larger percentage of polynuclear cells was found in the second sample than in the first, it was considered to indicate a more extensive or a more recent affection of the brain than of the cord. When little or no difference between the two counts was observed, a general involvement of the brain and cord alike was diagnosed. These conclusions were fully proved by the appearances of the cases which came to post mortem, details of which are given below.

Case CVIII.—Polynuclear percentage equal in the two portions of fluid on the day before death. Post mortem: purulent exudate was found both on brain and cord. The equal percentage is taken to indicate the general infection.

Case XC.—Differential count made four days, three days, and two days before death respectively. The polynuclear percentage was higher in each

instance in the latter portion of the fluid than in the first portion. At the post mortem a general infection of the brain and cord was found, but the pus on the vertex of the brain was more recent than elsewhere. It is suggested that the high percentage of polynuclears in the second portions of the fluid indicated the vertical extension of the exudate.

Case XCVII.—On the forty-ninth day of illness, polynuclear cells 74 per cent. in first portion of fluid and 80 per cent. in second. Marked hydrocephalus, with some old exudate at base of brain, found post mortem. The greater percentage in the second count than in the first is taken to indicate the persistence of exudate at the base of the brain.

The details of other cases will be seen in Table VIII.

TABLE VIII.—Contrasting the polynuclear percentage in the fluid at various periods of the disease with the post-mortem appearances.

Case.	Age.	Date of Punctures.	Date of Post mortem.	Polynuclear Percentage.		Appearance of Spinal Cord.	Appearance of Brain.
				1st portion	2nd portion		
XC	8	18.11.07	22.11.07	94	97	Bathed in pus	Extensive purulent exudate on vertex and at base
		19.11.07		96	98		
		20.11.07		97	99		
CVIII	1½	12.11.07	14.11.07	98	96	Numerous patchy areas of exudate	Extensive exudate, vertical and basal
		13.11.07		96	96		
XXXIV	17	21.12.07	14.1.08	97	89	Free from exudate	Organizing exudate at base; pus extending up Sylvian fissures
		22.12.07		80	69		
		23.12.07		86	85		
		26.12.07		80	89		
		27.12.07		90	91		
		2.1.08		91	92		
		5.1.08		97	97		
LXXVI	45	9.1.08	1.8.07	98	98	Organizing exudate on whole extent	Pus on vertex; exudate organizing at base
		27.7.07		96	89		
		30.7.07		90	93		
XCVII	3½	22.6.07	5.8.07	74	80	Free	Traces of exudate at base; ventricles greatly distended
LXII	10	13.7.07	19.8.07	73	85	Free	Ventricles greatly distended; faint traces of exudate at base
		4.8.07		52	63		
LXXV	35	6.9.07	11.9.07	92	89	Surrounded by organizing exudate	Exudate organizing at base; pus extending up vertex
		10.9.07		96	98		

The fluid in tuberculous meningitis contains cells which are usually entirely mononuclear. These cells are never present in such large numbers as to cause more than an opalescence in the fluid, and even this occurrence is rare; the majority of the fluids being nearly clear in appearance. The comparative frequency of an entirely mononuclear cell content will be seen from Table IX. The polynuclear percentage was estimated in 112 specimens. In seven cases no polymorphs were seen. Polynuclear cells were present in a ratio of from 1 per cent. to 10 per cent. in forty-two cases. In fifteen cases the percentage was between 11 and 20. Eight cases showed a percentage of from 21 to 30, five

TABLE IX.—Showing the polynuclear percentage, the amount of albumin, the degree of opalescence, and the occurrence of tubercle bacilli and endothelial cells in the fluid from sixty cases of tuberculous meningitis.

P = Polynuclears. TB = Tubercle bacilli. O = Opalescence. A = Albumin. E = Endothelial.											
Tubercle bacilli: A = Abundant, V = Very, F = Fairly, S = Scanty. Opalescence: SO = Slightly Opalescent, NC = Nearly clear. Endothelial cells: A = Abundant, V = Very, S = Scanty.											
Case	P	TB	O	A	E	Case	P	TB	O	A	E
Last day.											
II	0	FA	NC	2½	S	IV	27	S	NC	1½	VA
VII	84	VA	SO	1½	A	VIII	8	S	NC	3	A
VIII	0	0	NC	14	A	IX	94	S	O	2½	A
XXV	9	0	SO	1½	A	XVII	14	0	NC	5½	A
XXVI	2	0	NC	1½	VA	XXI	13	VS	SO	3	A
XXXIV	0	VA	NC	8	VA	XXV	0	0	SO	3	A
XXXVI	10	FA	NC	1	A	XXVI	6	VS	NC	2	A
XXXIX	0	A	NC	14	A	XXIX	0	S	NC	1	A
XL	5	VA	NC	1	VA	XXXI	20	VS	SO	8½	A
XLIV	6	A	SO	5½	A	XXXVI	10	S	NC	1½	A
XLVI	0	FA	NC	2	S	XXXVIII	60	VA	NC	1½	A
LVII	2	A	NC	2	VA	XXXIX	0	FA	NC	1½	A
LI						XLII	72	0	NC	3½	A
2nd last day.											
						XLIV	15	8	FA	SO	10
						XLV	2	S	NC	10	A
						L	0	FA	NC	1½	A
						LI	2	S	NC	2	A
						LII	54	0	NC	2	A
						LIV	0	S	NC	3½	A
						LV	60	VA	SO	2½	A
						LVI	10	0	SO	2	A
						LVII	20	A	NC	2	A
						LX	20	VA	NC	1	A
						I			NC	1½	A
3rd last day.											
						I	20	FA	NC	2	A
						V	75	VS	NC	2½	A
						VII	5	0	NC	1½	A
						VIII	0	0	NC	3	A
						XIV	25	0	NC	1½	A
						XVI	0	FA	NC	1½	A
						XIX	9	FA	SO	2½	A
						XXI	3	FA	NC	1	A
						XXVI	0	0	NC	5½	A
						XXXIV	2	S	NC	2½	A
						XXXVI	12	S	NC	1	A
						XXXIX	5	VA	NC	1	A
						XL	12	S	NC	1	A
						XL	6	VA	NC	2½	A
						XLIII	20	FA	SO	2½	A
						XLIV	0	0	NC	1½	A
						XLVIII	8	VS	NC	1½	A
						XLIX	0	0	NC	1½	A
						LI	8	A	NC	2½	A
						LIII	0	FA	NC	2½	A
						LVIII			NC		A
4th last day.											
						VI	0	S	NC	3	A
						VIII	91	VS	NC	1½	A
						IX	2	VA	NC	1½	A
						XII	3	0	NC	2½	A
						XXVI	8	A	SO	1½	A
						XXXI	3	FA	NC	1	A
						XXXIII	6	0	NC	1	A
						XXXIV	0	S	NC	1½	A
						XXXIX	15	VA	NC	1½	A
						XL	12	S	NC	2½	A
						XLII	0	FA	NC	1½	A
						XLIV	25	0	SO	1½	A

cases between 31 and 40, and one case, 43. Three cases showed a percentage between 50 and 60, and other three cases between 61 and 80. The percentage in four cases was 84, 91, 94 and 99 respectively. Thus in 88 out of 112 specimens of fluid, the percentage of mononuclear cells was between 80 and 100. To this number must be added about fifty more cases, in which the estimations were not accurately made but were noted as having an entirely mononuclear exudate.

The significance of a high percentage of polymorphonuclear leucocytes in the tuberculous fluids was not ascertained. It was noted, however, that tubercle bacilli were abundantly present in the fluid in eight out of ten cases in which the polynuclears were over 50 per cent. Little or no fluctuation in the proportion of the cells, in the majority of the individual cases, was observed. Such variations as did occur were irregular and sometimes considerable (Table IX). A high polynuclear percentage was only observed during the last week of illness. The highest percentage was 99 on the seventh last day of illness. In the three examples of the acute type of meningitis with the viscid fluid before mentioned, the exudate was mononuclear in all the samples of fluid.

TABLE X.—Showing the divisions of the nucleus in the leucocytes in the cerebro-spinal fluid on different days of the disease in cerebro-spinal fever.

	Day of Disease.	Divisions of Nucleus.
Case LXXII—Recovery	5th	3 4
	8th	3 4
	12th	3 4
	16th	3 4
	20th	3 4
Case LX—Recovery	6th	2 3 4
	12th	2 3
Case XXXVI—Death	4th	3 4 5
	9th	4 5 6
	12th	4 5 6
Case CV—Death	14th	4 5
	15th	4 5
	16th	4 5 6
	18th	4 5 6
	20th	4 5 6
	20th	4 5 6
Case LXIV—Death	5th	3 4 5 6
	6th	3 4 5 6
	7th	4 5 6
	12th	4 5 6
	15th	4 5 6

Arneth has pointed out that the more active phagocytic leucocytes may be distinguished from the less active forms by the shape of the nucleus. In the latter the nucleus is much subdivided, while in the former it is more or less of a horseshoe shape. He states that the active cells are present when the inflammatory process is being successfully overcome, and the multipartite forms are found in a persisting or chronic infection. The results of the present series of observations support Arneth's theory. In the first few days of illness in cerebro-spinal fever the bulk of the polynuclears in the fluid have a bipartite or

tripartite nucleus, and in the cases which recover early these are the types of leucocytes met with from day to day. If, however, the disease continues acutely, to end in death or to become chronic after a period, the percentage of multi-nucleated cells increases. In some instances the nucleus in the majority of the cells consisted of five to seven parts. In those chronic cases which recovered ultimately, the multi-nucleated cells were found all through, and were not replaced at any time by the more active forms of leucocytes. Cells with a horse-shoe-shaped nucleus were not commonly seen at any time (Table X).

The Endothelial Cells.

Endothelial cells are found more or less abundantly in the fluid at all stages of meningitis. They are shed from the pia-arachnoid and the dura mater as a result of the inflammation. Their presence in large or small numbers is an indication of the severity and extent of the meningeal affection. They are not readily confused with the other cells in the fluid. Endothelial cells are larger than the leucocytes, and their staining properties are different. They are recognized by their large size and their cubical or hexagonal shape. The nucleus is comparatively large, always elongated, and, in the degenerated forms, often has a tailed appearance. The amount of protoplasm is small and forms a narrow ring round the nucleus. In the great bulk of the cases, however, the protoplasm has disintegrated, and only the large nucleus remains. With Leishman's stain the nucleus is of a purple or mauve colour, and the chromatin network is distinctly visible. The surrounding protoplasm stains a faint blue. In the acute pyogenic varieties of meningitis, the endothelial cells vary in number at different stages of the disease. Even in those cases which progressed uniformly towards recovery within limits of a few weeks this was observed, and in the more chronic cases a distinct tendency to periodic increase was found to follow more or less closely an aggravation or an extension of the disease.

Actual counts of the number of endothelial cells were not made, but their relative proportion was noted in the cases from time to time. The three cases which were punctured during the first day of illness showed a small number of these cells. In the two cases examined at the end of the first day, they were also few in number. Marked differences were observed between the smears from the seventeen cases on the second day. The turbidity is of an extreme degree in most instances at this time, and the polynuclear cells are in such abundance that the desquamated cells, although present in large numbers, might appear relatively few. They were noted as very abundant in one case, abundant in eight, and sparse in nine. Three out of the seventeen cases recovered, the endothelial cells being sparse in two. In the seventeen samples of fluid which were examined on the third day, an almost identical condition was found, and other two cases which eventually recovered showed a small number of endothelials.

From the fourth day of illness onwards, when the turbidity has begun to lessen, these cells are observed in greater numbers, but it is not until the later

stages of the disease, when a slight turbidity or an opalescence has become established, that the periodic fluctuations of the endothelial cells are observed. An increase in the number of the endothelial cells is also observed during early convalescence, before the fluid has entirely cleared. This increase is always associated with a decrease in the percentage of polymorphs, and is probably due to the regenerating endothelium shedding the cells which have been injured during the disease. In these circumstances small groups or plaques of cells may be seen.

In cases of tuberculous meningitis the endothelial cells are always present in fairly large numbers. This may be due to the small total number of cells in the exudate. They are, however, not so easily differentiated except by their size, on account of the presence in considerable numbers of large mononuclear cells from the blood. An increase of the endothelial cells is always found as the disease progresses. The numbers do not fluctuate as they do in the acute pyogenic cases, and the steady increase coincides with the extension of the disease.

The Staining Properties of the Cells as regards freshness or degeneration.

The staining properties of the polynuclear cells vary at the different stages of meningitis. In the very early period of the disease the cells are comparatively fresh and they take up stains well, but at later periods they become more or less degenerate, so that they stain faintly and unevenly. In the fresh condition the cell outline is regular and the contour clear. The nucleus is easily differentiated from the surrounding protoplasm by the staining method used, and the colours are well taken up. The degenerated cells, on the other hand, present a more or less faint outline of irregular shape, and the cell structure is altered. The stain is diffused unequally, and may be very poorly taken up. The protoplasm in most instances has either disappeared in these degenerated forms, or only a faint halo remains. The nucleus also is much broken up and drawn out into threads. In this condition the shreds of nucleus stain a pale mauve, and the protoplasm, if present, is of a slightly green or blue tint.

The condition of the cells shown in this way indicates to a certain extent the progress of the disease. At the commencement of the infection, leucocytes migrate in great numbers from the blood stream and are found fresh in the cerebro-spinal fluid. After a period, depending on the severity of the infection, degenerative changes appear, as shown by their altered staining qualities. These changes are confined mainly to the polymorphonuclear cells.

At the early stages of cerebro-spinal fever the cells present similar appearances, but as the disease continues or when remissions occur, fresh leucocytes are again found mixed with the degenerated cells, and these appearances are of considerable prognostic value. In the acute cases which terminate within a few days by crisis, the cells are found progressively more degenerated from day to

day, and no fresh forms are observed. When, however, the disease becomes more or less chronic, as usually happens, fresh cells are seen amongst the older elements from time to time, associated with a persistence or a recrudescence of the inflammation. This admixture of comparatively fresh and degenerated cells was uniformly observed in the chronic stages of cerebro-spinal fever. A certain proportion of fresh cells is observed in most of the cases, apart from a recrudescence of the disease, but in large numbers their presence is always an unfavourable sign, indicating a spread of the infection. An increased polynuclear percentage is always associated with the appearance of the fresh cells.

Several specimens of turbid fluid, containing fairly fresh leucocytes and organisms, were allowed to incubate at blood heat for definite periods of time. Smears were made at the end of one hour, two hours, four, six, twelve, eighteen, and twenty-four hours. By the end of four hours, degenerative changes were seen, more especially in the presence of a large number of organisms. In from eighteen to twenty-four hours only a homogeneous mass remained, which stained a faint mauve colour by Leishman's method.

In comparing the staining reaction of the cells in different cases, and even in the same case at different periods of the disease, the virulence of the cell-poison must be taken into account. When rapid degeneration of the cells occurs it indicates a very acute inflammation. This is usually found in the earlier stages of the disease, but in the later periods comparatively little change may be seen for several days, and old degenerated forms may persist for a long time.

The cellular elements in tuberculous meningitis do not show these differences to the same extent. Degenerated forms are rarely seen; indeed, the uniformity of the appearances of the cells and their comparative freshness are obvious features in all the cases. Even in those instances where a large polynuclear percentage occurs, the leucocytes show little or no change from time to time.

The Organisms.

These observations only deal with the characters of the meningococcus in the cerebro-spinal fluid, and it is not intended to enter into the question of its behaviour outside of the human body. As regards the other organisms which were found in a few of the acute pyogenic cases—pneumococci and streptococci in pure culture, and pneumococci and staphylococci in mixed infection—it was only noted that they were present in great abundance in the smears, were almost entirely extra-cellular, and gave rapid and profuse growths when cultivated.

Normal cerebro-spinal fluid is a good culture medium for various organisms, as judged by their rapid growth when allowed to incubate for a time. When, as occurs in meningitis, the fluid contains an appreciable quantity of albumin, its efficiency as a culture medium is increased. The rapid extension and the extreme fatality of pyogenic meningitis may be in part attributed to this cause. In those cases of cerebro-spinal fever which proceed early to a favourable termination, the meningococcus passes through a definite cycle of changes. At

the onset of the disease the organisms are extra-cellular. After a short period some are observed to be taken up by the leucocytes. At a later stage the majority are intracellular, and only a small number found free in the fluid. These latter forms tend to disappear entirely, and the last stage is the digestion of the intracellular organisms. This chain of events, however, is exceptionally observed. In the majority of the cases the cycle was broken at various times.

Observations were made with regard to the number of organisms seen in stained smears, and also with regard to the relative proportion of those situated inside and outside of the leucocytes, from day to day. The numbers are classified as 'sparse', 'abundant', and 'very abundant'. The organism was found in all the cases which are included in the series. In certain cases, however, it is only recovered by cultivation of the fluid, and in other instances it is only seen in the smears on rare occasions. In Case XVII meningococci were only seen in stained smears on the seventeenth day of the disease. Ten punctures, beginning on the second day of the disease, were performed on this patient during an illness which lasted for two months. In Case XIX the organism was not seen in the stained smears during life, but was cultivated from the fluid, and was seen in the exudation examined post mortem. This patient suffered from an acute attack which ended fatally on the seventh day. The fluid obtained by puncture on the second and fourth days of the disease was very turbid, with a high percentage of polynuclear cells. In Case LXXXVI no organisms were seen microscopically at any period of the disease, but on three occasions cultures from the fluid were positive. This patient was admitted on the eighth day of illness. Eight punctures in all were made, the last on the twenty-fourth day, when all signs of inflammation had subsided. The illness was comparatively mild, and was associated with an opalescent fluid.

In other two cases, which were only included in this series at a late period of the disease, organisms were not seen, but had been found by other observers at earlier date. It may be stated, then, that in only one case out of the total number examined at a reasonably early period of the disease, were no organisms seen microscopically during the life of the patient. The details of the observations are tabulated (see Table VII). In the three cases which were punctured during the first day of illness, organisms were not seen in two, and in the third they were abundant and mainly extra-cellular. In the two cases examined at the end of the first day they were abundant extra-cellularly and intracellularly in one, and in the other they were less numerous and mainly intracellular. Out of seventeen smears examined on the second day, organisms were not seen in six. In five the numbers were sparse both outside of and inside of the cells. In three sparse extra-cellular diplococci were found, and in other three cases they were fairly abundant within the cells but sparsely extra-cellular. Greater differences were observed in the seventeen smears examined on the third day of illness, and on each succeeding day the disposition of the organisms in individual cases was more variable. A certain amount of similarity, however, is to be seen in cases of the same type of the disease. In the acute cases which end by crisis,

the organism passes through the cycle of changes already described, with perhaps occasional remissions. Those very acute cases which run a rapid course are characterized by a fair abundance of organisms, and death usually results before the intracellular stage is reached. The cases which have become chronic, however, show widely different appearances, and the organism tends to remain extra-cellular in greater or lesser number throughout the disease. The presence of the extra-cellular forms at a late period of the illness, after the intracellular stage has been reached, indicates a recrudescence of the infection, and is usually associated with a rise of temperature and an increase of turbidity. The most favourable cases are those in which the organisms are few in number, and are rapidly ingested by the leucocytes. The unfavourable signs are abundance of the organisms and persistence of the extra-cellular element.

The meningococcus may persist in the cerebro-spinal fluid for long periods. In Case CXI intracellular organisms were found on the 147th day of illness, and on the 170th day cultures from the fluid were positive. In another case (V.M., aged 3 years, not included in the series), intracellular diplococci were present on the 244th day of the disease, and on the 281st day the culture from the fluid was positive.

TABLE XI.—Showing the change in number and position of the organisms from day to day with regard to the leucocytes in the cerebro-spinal fluid.

E = extra-cellular, S = single, M = multiple, C = crowded (very numerous), s = sparse, a = abundant, v = very.

Case LXXII—Recovery				Case CV—Death			
5th day	Es			14th day	Es	Sa	Ma
8th "	Cs			15th "	10 a.m.	Es	Sa Ma
12th "	Es			" "	10 p.m.	Es	Sa Ma Ca
16th "	Ea	Ss	Ms	16th "	Ea	Sa	Ms Cs
				18th "	Es	Sa	Ma Ca
				20th "	Es	Sa	Ma Ca
Case LXVI—Death				Case CIV—Death			
5th day	Es	Sa	Ma Ca	6th day	Es		
6th "	Es	Sa	Ma Ca	8th "	Ea		
7th "	Es	Sa		13th "	Ea	Ma	Ca
15th "	Ss			21st "	Ea	Sa	Ma Ca
18th "	Es			24th "	Eva	Sa	Ma Ca
45th "	Sa	Ma	Ca	27th "	Eva	Sa	Ma Ca
46th "	Ma	Ca		31st "	Es	Sa	Ma Ca
47th "	Ma			35th "	Es	Sa	Ma
Case XXX—Death				40th "	Es	Sa	Ma
3rd day	Ea	Sa	Cs	47th "	Ea	Sa	Ma Ca
4th "	Es	Ss	Ma Ca	50th "	Es	Ss	Ms Cs
5th "	Ea	Sa	Ca	55th "	Cs		
6th "	Ea	Ss	Ca	59th "	Ms		
7th "	Ea	Ca		65th "	0		
Case XI—Death							
2nd day	Ea	Ss					
3rd "	10 a.m.	Es	Sa				
" "	10 p.m.	Es	Sa Ma				

The change in the nature of the organism in the late chronic stages of cerebro-spinal fever has already been described in connexion with the presence of sugar in the fluid. Table XI shows the results in six cases (comprising forty specimens of fluid) of more accurate observations on the disposition of the organism at various stages of the disease. In this series special note was made of the number of intracellular organisms. The terms used were 'single', denoting one pair of diplococci in a leucocyte, 'multiple', including any number from two to eight, and 'very numerous', when the number was above ten. The last condition, namely, the 'very numerous', was not commonly observed. It occurred in less than fifty specimens out of over 1,000. These fifty smears were obtained from eight cases at comparatively early stages of the disease. It was not found later than the first month of illness. Only one of the cases recovered, so that, although the presence of an opsonin to a satisfactory extent is indicated, it is not necessarily a favourable sign. In several instances the opsonic value of the cerebro-spinal fluid was estimated both in the earlier and the later periods of the disease. This was found to be very low, and the results are in agreement with those of other observers. The 'single' condition was the most commonly met with, especially in the more chronic cases. In the acute stages leucocytes containing one pair of organisms and others with several pairs were frequently seen.

Tubercle bacilli were found in the great majority of the fluids from cases of tuberculous meningitis, and careful search was made for the organism in fifty-seven cases. The fluid was centrifugalized soon after its withdrawal, before the coagulum had formed. Similar amounts were used as far as was practicable, and the same duration and speed of centrifugalization was given to each specimen, in order that reasonably comparable results might be obtained. The organism was found in forty-nine out of the fifty-seven cases so treated. One hundred and fourteen specimens of fluid were obtained from these cases, and the tubercle bacillus was detected in eighty-two. The eight cases (comprising thirty-two samples of fluid), in which a negative result was obtained, included five which were only punctured on one occasion, two which were punctured twice, and one three times, giving a total of twelve samples of fluid. The remaining twenty samples, in which no organisms were found, were obtained from cases in which a positive result was obtained on other occasions. Table IX shows these results.

Twelve cases were punctured on the day of death, tubercle bacilli being found in nine. On the day before death twenty-three specimens were examined, the result being positive in seventeen. In twenty-two cases, two days before death, organisms were present in sixteen. Thirteen fluids were examined on the fourth last day with a positive result in nine, and on the fifth last day organisms were present in nine out of eleven cases. It will be seen that the bacilli tend to become more numerous as the day of death approaches, but it is in the individual cases that the tendency to increase is most noticeable.

In view of the fact that tuberculous meningitis more commonly affects the brain than the cord, the fluid was drawn off in several portions in order to

ascertain whether or not the organisms were more numerous in the later portions than in the first. Table XII shows these results, and it will be seen that little consistent difference was observed between the numbers in the separate samples. No relation between the number of the organisms and the other conditions in the fluid, such as the amount of albumin, was observed, but it was noted that the bacilli were numerous in those cases where there was a high polynuclear percentage. The bacilli were uniformly extra-cellular except in one instance (Case LV). In this patient the polynuclear percentage was 60, and the organisms were very abundant.

TABLE XII.—Showing relative frequency of organisms in separate portions of fluid in cases of tuberculous meningitis.

S = sparse, A = abundant, V = very, F = fairly.

		1st Portion.	2nd Portion.
Case XLIV	10th last day	3	11
	9th "	0 2	7 9 0 0
	8th "	7	8 13
	7th "	10	7
	6th "	17	0 32
	5th "	21	35 25
	4th "	130	182
	Last day	547	454

In this case a rough count was made of the number of organisms seen in traversing the same extent of field.

		1st Portion.	2nd Portion.
Case XXXI	5th last day	0	S
Case VIII	4th "	0	S
Case XLVII	5th "	FA	FA
Case XXVI	3rd "	VS	0
Case IX	6th "	VS	0
	4th "	0	S
	2nd "	S	S
Case VII	14th "	0	0

The Crystals.

Crystals formed by evaporating portions of the fluid are found in both the acute pyogenic and the tuberculous forms of meningitis. The commonest are those of the stellar phosphates. But in the fluid in cases of tuberculous meningitis are certain crystals which do not occur in the acute infections. These crystals are minute, square or diamond-shaped bodies, colourless, highly refractile, and with a double outline. They do not appear to be of the nature of choline or of cholesterin. They were carefully searched for in numerous samples of fluid in cerebro-spinal fever, but were never found in that disease. Up to the present moment their exact nature has not been ascertained. Occurring as they

do only in tuberculous meningitis, they are a valuable aid in the diagnosis of that disease, especially when tubercle bacilli are not found. They occurred in 56 out of 109 specimens of fluid. The subject is still under consideration, and the result will be published in due course.

Conclusions.

A routine examination of the fluid which is drawn off by lumbar puncture in cases of meningitis is to be recommended. The operation itself causes only momentary pain, and, with suitable precautions, is not productive of harmful results. Opportunities of collecting fluid are now more frequent in view of the present mode of treatment in cerebro-spinal fever by intraspinal injections of Flexner's serum.

The progress of the infection, both in the acute pyogenic and the tuberculous forms of meningitis, is indicated by the changes in the cerebro-spinal fluid, and a proper interpretation of the observations is of great value in prognosis and diagnosis.

These observations are important in connexion with the therapeutic effect of the withdrawal of fluid by lumbar puncture. Few facts are known regarding the circulation of the cerebro-spinal fluid in diseased conditions of the meninges, and in the present state of knowledge the only reliable means of estimating the value of lumbar puncture is to note its effect on the patient. The withdrawal of fluid from cases of cerebro-spinal fever is usually attended with beneficial results. The intracranial pressure is reduced and fresh fluid is formed to dilute the infective material. In the early stages of the disease there is great relief to the symptoms, and in the later stages the operation tends to prevent the onset or check the progress of hydrocephalus. In tuberculous meningitis, on the other hand, the most that can be attained is an amelioration of the headache and restlessness. Forty-three observations were made with the manometer. The highest pressure was met with in the early stages of cerebro-spinal fever. It was also found that the fluid reaccumulates rapidly, the pressure rising above normal again within a few hours. An increased intracranial pressure was proved to exist throughout the whole course of meningitis, and to persist for some time after the inflammatory condition had subsided in those cases which recovered.

In meningitis from any cause, the normal transparency of the cerebro-spinal fluid is lost. A decided turbidity is significant of an extensive purulent exudate. In a few instances a yellow turbid fluid changes to a thick pus. Organization and absorption of the inflammatory material are indicated by a clearing up of the fluid. An extension of the disease is always accompanied by an increase of the turbidity. As long as some exudate remains some opalescence persists, and a turbidity may be present at a very late stage of the illness, in which case it is usually associated with hydrocephalus. It is possible

in some instances to estimate the site or the extent of the exudate by comparing the degree of turbidity in different samples of fluid collected at the same time from the patient. The degree of turbidity along with the height of the pyrexia are reliable guides to the progress of the disease. The fluid in tuberculous meningitis never becomes turbid, and the great majority of the samples are nearly clear in appearance.

A yellowish or greenish colour in a turbid fluid occurs in the early stages of cerebro-spinal fever. It indicates an active and extensive process. When organization of the exudate is proceeding, or when the inflammatory condition is mild, a white turbidity is observed. Straw colours and reddish brown or olive tints are seen in opalescent or nearly clear fluids when bleeding has previously been caused, or where the inflammation is of a haemorrhagic character. The fluid in tuberculous meningitis is always colourless unless there has been some admixture with blood.

The majority of the fluids possess very little viscosity even when considerable turbidity is present. Actual pus is comparatively rarely met with, and it is to be regarded as a result of a more advanced condition than that indicated by a yellow turbid fluid. A hitherto undescribed type of meningitis occurs which is characterized by a somewhat viscid fluid resembling a plastic effusion. It is found both in cerebro-spinal fever and in tuberculous meningitis, and it is always associated with a high percentage of albumen and a rapidly forming, jelly-like clot.

The estimation of the specific gravity is of little practical value on account of the small range of variation in the one patient at different stages of the disease. Exceptionally a high reading occurs in the acute haemorrhagic types of fluid.

The clots have been classified according to their appearance as coarse cobweb, delicate fibrillar, and fine cotton-wool. The first occurs in a turbid fluid, the second form is found when the fluid is opalescent, and the third is characteristic of a clear or nearly clear fluid. Two other varieties are met with, a jelly-like clot found in viscid fluids and innumerable small separate shreds of fibrin, when the meningitis is subacute or chronic. These two types are comparatively rare. A coagulum is one of the earliest signs of meningeal inflammation, and it is the last pathological sign to disappear in those cases which recover. The coarse cobweb variety is never found in tuberculous meningitis nor do the separate shreds of fibrin occur, but all the other forms exist.

A sediment is only observed in yellow turbid fluids. Consequently, it seldom occurs except in the early stages of acute pyogenic meningitis, when there is extensive and recent involvement of the spinal cord.

The fluid in acute pyogenic meningitis is always alkaline, but the degree of alkalinity is less than that of normal fluid. It has been proved by original experiments that the decrease in alkalinity is the result of the neutralizing action of the lactic acid which is formed by the meningococcus breaking up the dextrose

normally present in the cerebro-spinal fluid. The more nearly normal degree of alkalinity which is found in some of the cases in the late chronic stages of cerebro-spinal fever has also been shown to depend on an alteration in the nature of the diplococcus when it loses its power of breaking up the sugar. The fluid from cases of tuberculous meningitis shows the greatest degree of alkalinity, being often almost equal to the normal. The least degree is found in the fluid from acute cerebro-spinal fever. In the chronic stages of that disease, however, the alkalinity is only slightly less than that in the tuberculous fluids.

An appreciable quantity of albumin is always present in the fluid from cases of meningitis. It is advisable to estimate the amount by direct measurement. The acuteness of the meningeal inflammation can be fairly accurately gauged by the percentage of albumin. It is a hopeful sign when the amount of albumin decreases during the course of the illness. A tendency to increase is manifested in the later stages of cerebro-spinal fever, when hydrocephalus is established. A very high percentage of albumin is present in the viscid type of fluids. In the tuberculous cases the amount of albumin varies in an irregular manner, and it is of little prognostic value in this variety of meningitis.

The absence of reducing sugar from the cerebro-spinal fluid is pathognomonic of meningitis. Sugar, however, is not absent at all stages of cerebro-spinal fever, and during the chronic periods of the disease Fehling's solution may be reduced in the presence of living organisms. It may be said, however, with certain reservations that the reappearance of the sugar is an indication that the disease is in process of cure. In tuberculous meningitis sugar is very rarely entirely absent from the fluid.

The cellular content in cases of meningitis is greatly increased above the normal. The increase is mainly due to the excess of polymorphonuclear cells in cerebro-spinal fever. It is advisable to make differential counts in each case. The percentage of polynuclears depends on the acuteness of the inflammation. As the disease subsides the percentage decreases, and the remissions throughout the course of the illness are associated with an increase in the proportion of the polymorphs. At the termination of the illness the mononuclear cells are predominant, and they persist above the normal proportions for some time after convalescence is established. The polymorphonuclear cells may disappear very rapidly from the fluid in the acute abortive cases, and they may be found abundantly at very late periods in the chronic types of the disease. In tuberculous meningitis the cells are mainly mononuclear. Rarely a high percentage of polymorphs is met with. The proportion of the two kinds of cells does not alter in the same manner as it does in the acute infections.

The endothelial cells indicate the presence of meningitis. Their number depends on the severity of the inflammation. In the acute cases of cerebro-spinal fever, after the first few days, large numbers are found. The number fluctuates thereafter, and always increases after an extension or aggravation of the disease. When the infective process is at an end very large numbers, sometimes cemented together, are found in the fluid, indicating the termination of

the disease. In the tuberculous fluids comparatively large numbers of endothelial cells occur, and there is a regular increase as the disease progresses.

The freshness or degeneration of the polynuclear cells is dependent on the stage and the severity of the infection. At later stages of the disease in cerebro-spinal fever, a mixture of fresh and old forms is commonly met with. This always indicates a persistence of the exudate or a spread of the infection. In tuberculous meningitis the cells remain comparatively fresh for long periods, and old forms amongst the fresh cells are exceptionally seen.

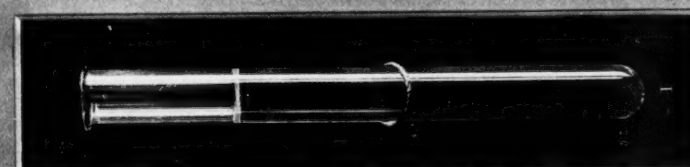
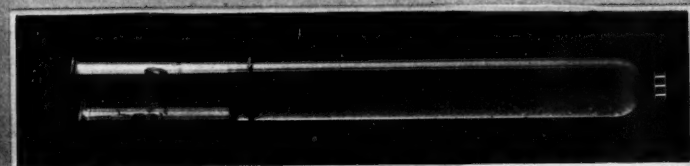
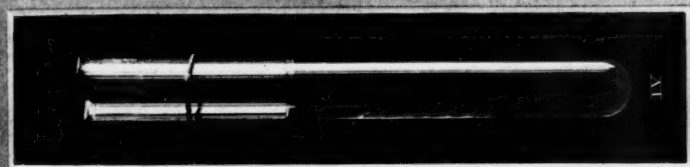
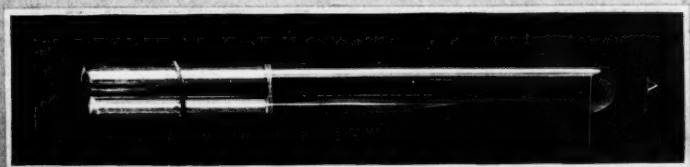
The meningococcus passes through a definite cycle of changes in the simple acute cases, being at first extra-cellular and latterly becoming ingested by the leucocytes. This occurrence, however, is exceptional, and in most cases the chain of events is broken from time to time during the remissions which characterize the disease. The presence of organisms in large numbers is an unfavourable sign, and a persistence of the extra-cellular condition is seen in the cases which end fatally. Death may, however, ensue even when the majority of the bacilli are intracellular. The organism may be found in the fluid at very late periods of cerebro-spinal fever. The tubercle bacillus can be demonstrated in the fluid in the great majority of the cases of tuberculous meningitis. The organisms tend to increase in number as the disease progresses.

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DESCRIPTION OF FIGURES.

- FIG. I. Opalescent fluid with a clear layer at the top, proving that clot formation is late.
FIG. II. Scanty fine fibrillar coagulum in a slightly opalescent fluid.
FIG. III. Sparse cotton-wool coagulum.
FIG. IV. Invisible coagulum. The fluid has been gently shaken so that a fine thread is seen at the surface. Throughout the fluid is an extensive transparent clot.
FIG. V. Unusual type of coagulum. Very numerous and minute shreds of fibrin.



CONCERNING INTERMITTENT HYDRARTHROSIS

By ARCHIBALD E. GARROD.

Of periodicity in disease no more striking example can be quoted than the recurrent effusion into joints, with little or no febrile disturbance or local signs of inflammation, which goes by the name of intermittent hydrarthrosis. The intervals between the successive attacks are, as a rule, so regular that the patients can foretell with accuracy the day, and sometimes even the hour, when a recurrence is to be expected, and can make their arrangements accordingly.

More than sixty years have elapsed since Perrin (1) first recorded such a case, and some seventy other examples have since been described, but we appear to be as far removed as ever from a satisfactory explanation of the phenomenon. The study of such cases has revealed links connecting intermittent hydrarthrosis and certain other morbid conditions which sometimes exhibit a similar periodicity, but has not explained the periodicity itself.

The no less striking periodicity of malarial attacks, long equally obscure, has found a simple explanation in events in the life-history of certain haematozoa; but here the periodicity is inherent in the parasite, and is merely reflected in the symptoms exhibited by the host. It is little likely that a similar explanation applies to intermittent hydrarthrosis, in which the periods do not conform to a few definite types, tertian or quartan, as do those of ague, but differ widely in individual cases. Benda (2), from a study of recorded examples, concludes that the commonest periods lie between eight and eleven days from the beginning of one attack to that of the next, but sometimes the intervals are much shorter, and occasionally they are as long as three weeks, a month, or even three months.

When, in any case, two or more cycles run concurrently in different joints, the cycles tend to be of the same length, and it is difficult to resist the conclusion that the length of the cycle is a peculiarity of the individual sufferer rather than of the disease from which he suffers, being neither inherent in a parasite nor determined by external conditions.

That external, and especially seasonal, influences take part in the determination of the periodicity of some diseases is undoubted, as witness the annual returns of chronic bronchitis, and the winter attacks of paroxysmal haemoglobinuria; but if we exclude a case described by Féré (3), which cannot be regarded as belonging to the group under consideration, in which attacks of hydrarthrosis,

attended by urticaria, were always determined by quarrels with a fellow inmate of an asylum and ceased when the provoking agent left the institution, there is no evidence of the influence of outside agencies in causing the returns of intermittent hydrarthrosis.

Those who have written on the subject agree in grouping the cases of intermittent hydrarthrosis into two classes, styled primary and symptomatic respectively. In primary cases the periodic swelling comes on as an isolated event, sometimes after an injury, and the affected joints, which are in the great majority of instances the knees, recover completely or almost completely in the intervals, at any rate in the earlier stages. In symptomatic cases, on the other hand, the affected joints have already been damaged, more or less severely, by antecedent disease, such as the more obstinate forms of gonorrhoeal arthritis, or the crippling lesions of many joints commonly classed as rheumatoid arthritis or arthritis deformans. In other respects the cases of the two classes closely resemble each other, and the observation of a series of examples inclines one to the opinion that, as Linberger (4) maintains, intermittent hydrarthrosis is a phase or symptom of various articular lesions, rather than a disease *sui generis*.

My own experience, which embraces eight cases, differs from that of most of those who have written on the condition, in that the majority of my cases (five out of eight) have been of the symptomatic kind.

In the present paper I shall not attempt to do more than to call attention to and discuss certain special points of interest which some of these cases present. One of them throws important light upon the morbid associations of intermittent hydrarthrosis, and in two others such careful records of individual attacks have been kept, by highly educated patients, that, thanks to these, I am able to illustrate the periodicity and its variations in a manner which has not hitherto been done.

The view which most commends itself, and of which Schlesinger (5) has been the chief exponent in some of the most valuable contributions yet made to our knowledge of the subject, regards intermittent hydrarthrosis as nearly akin to the acute circumscribed oedema described by Quinke (6), or, as Schlesinger would phrase it, as one of the manifestations of *hydrops hypostrophos*.

There is, indeed, much to suggest a kinship of certain articular lesions, of a transient character, with the cutaneous lesions of the erythema group. Articular pains are intimately associated with erythematous eruptions, as witness the clinical syndromes of Henoch's purpura and of erythema nodosum. The erythematous eruptions which not unfrequently develop in the course of rheumatic fever, of the marginate and papular varieties, and which may be classed as rheumatic rashes, find their special clinical associates in the articular lesions of that disease; whereas some other rheumatic manifestations, such as chorea and subcutaneous nodules, are specially associated with the cardiac troubles. Moreover, the transient character of the arthritis of true rheumatism, the conspicuous swelling of the joints, and the rapid subsidence of the attack

leaving no traces of its passage, justify the hypothesis that the arthritis of acute rheumatism is, in a sense, an erythema of the articular structures.

The same may be said of intermittent hydrarthrosis, although in most cases, but not in all, synovial effusion is its most conspicuous feature, whereas peri-articular swelling is trifling or wholly absent.

The evidence which has been adduced in favour of the affinity of the periodic joint affection with circumscribed oedema is, at the least, highly suggestive. There have been met with in association with the hydrarthrosis certain troubles with which circumscribed oedema also is apt to be associated. Some of the patients have suffered from urticaria of the ordinary kind. Asthma has been met with as an associate by Burchard (7), and other vasomotor disturbances, including polyuria coincident with the attacks, have also been observed. Several patients have suffered from exophthalmic goitre, and in a case of Homén's (8) such a patient exhibited at some times patches of circumscribed oedema and at others intermittent swelling of joints.

Circumscribed oedema sometimes exhibits periodicity, although it must be acknowledged that this is far from being a constant feature of the affection; but it must be remembered that only those rare cases of joint trouble in which there is periodicity are classed as examples of intermittent hydrarthrosis, whereas I am inclined to think that, in cases of chronic arthritis of various kinds, such transient attacks not unfrequently occur without any such regular periodicity.

The remarkable periodic vomiting of adults, also a rare symptom, is known to occur, as Strübing (9) showed, in direct association with angioneurotic oedema. In the earliest recorded cases of such vomiting, described by Adams (10) in 1817, the recurrences were as accurately periodic as those of intermittent hydrarthrosis. Moreover, Adams cured his patients with arsenic, which has been given with conspicuous success in some cases of the articular trouble. In Köster's (11) case the periodic swelling of the knee was preceded by headache and vomiting.

If intermittent hydrarthrosis be as closely allied to circumscribed oedema as has been suggested, the two phenomena should occur in the same individuals with sufficient frequency, or in sufficiently close association, to exclude a mere accidental concurrence. As a matter of fact there are several cases on record in which such an association has been observed.

To one of these, recorded by Homén, I have already alluded. Goix (12) described the case of a young woman, aged 26, whose right knee was the affected joint. On one occasion swelling of the right cheek accompanied that of the knee, and reached its maximum when the knee was already subsiding after an attack of unusually short duration. There was some toothache, but there were no carious teeth upon the affected side.

Köster's patient, who vomited before the articular attacks and had polyuria with them, occasionally had reddening, with a sensation of heat and tension, of one half of the face. Senator (13) saw intermittent hydrarthrosis in a boy of 17, who up to the age of 12 years had developed, every summer, a swelling in

the right gluteal region. In the original case of Perrin oedematous swellings appeared around many joints, but only a few were the seats of effusion.

On the other hand, Quinke (14), approaching the question from an opposite standpoint, mentions a case of acute circumscribed oedema in which effusions repeatedly developed in articular cavities; other writers also speak of such events.

Lastly, Féré (15) observed the case of an hysterical woman who at one time suffered from daily attacks, occurring in the early morning, in which there was blue oedema of the legs and swelling of the knees.

With the exception of the example last referred to, which did not in all respects conform to type, I know of no published case in which circumscribed oedema developed, time after time, in association with the attacks of hydrarthrosis and forming an integral part of the cycle. It is because such an intimate association of the two phenomena was observed in it, that the case now to be described acquires a special importance.

Case I. An unmarried lady, aged 46, gave the following history:—At the age of 14 she suffered from some form of articular trouble, which persisted for about a year, but from which she recovered completely. When about 21 years old she developed a painful swelling of the knee-joints, which had no intermittent character. Some years later the hip-joints were attacked, and many other articulations were in turn invaded, including those of the cervical spine and the temporo-maxillary joints. In the notes taken by my father, who saw her on one occasion in 1889, there is no mention of any periodicity. The periodic attacks were first noticed in the left hip, about ten or twelve years ago, when the crippling arthritis had already existed some fifteen years. The period was at that time some four days from onset to onset. Intermittent hydrarthrosis of the knees developed about a year before I first saw the patient, and still more recently it had extended to the right wrist also.

When seen she exhibited the characteristic appearance of a patient who was the victim of long-standing rheumatoid arthritis, save that the joints of the fingers were little affected. She walked with much difficulty with the aid of two sticks.

There were then two distinct cycles of intermittent hydrarthrosis. The pain, which was unusually severe, and swelling of the knees and right wrist occurred in quick succession at intervals of eight days, but sometimes the recurrence had been after four days, conforming to the original hip cycle. Two days after the attack in the knees and wrist the hips became affected, and the two cycles, although apparently independent, had exactly the same duration. Of late the hip attacks had not unfrequently been omitted.

Some months previously a fresh symptom had developed, and characteristic areas of circumscribed oedema of the lips or eyelids had accompanied the onset of the knee-wrist attacks. These swellings only lasted a few hours. With the hip attacks no such swellings developed.

The patient had always been subject to urticaria, and complained of a lumbar pain which came on at about 5 a.m. each day, and passed away by breakfast time.

The course of an attack was as follows:—On the morning of the day on which an attack was due the patient awoke with the right wrist swollen and painful; by the evening the right knee had become swollen, and next morning the left knee was similarly affected. Two days later first the right and afterwards the left hip was attacked. The affection of the knees and wrist had abated by the third day.

When seen on the second day of a knee-wrist attack, the right knee was swollen and felt hot; the synovial cavity was rather tensely distended with fluid. The left knee was much less swollen, and less hot, and when listened to with the stethoscope yielded a pronounced synovial crackle on movement. Two days later the fluid was almost gone from the right knee.

The original disease appeared to be still smouldering on. The fingers, which had previously escaped, had been attacked during the previous six months, and there was fusiform swelling, of the familiar kind, of the mid-joints of the right ring and index fingers. Pain was also complained of in the shoulders, the neck was stiff and the movements of the jaw limited, but none of these joints were the seats of periodic exacerbations.

There were no signs of visceral disease. The area of cardiac dullness was of normal extent; the first sound was slightly impure at the apex but there was no murmur. The impurity was apparently due to reduplication of the first sound.

Dyspepsia, from which the patient had formerly suffered, no longer troubled her.

She had taken guaiacol carbonate regularly for a year previously. Aspirin greatly relieved the pain and stiffness attending the periodic attacks.

Treatment with arsenic was initiated, and later the patient was treated at Harrogate, with cataphoresis of salicylic ions, by Dr. R. J. Morris. Whether as the result of treatment or no, the intermittent attacks of both cycles have now ceased, and the circumscribed oedema of the lips and eyelids also has wholly ceased. The only reminder is that she always has more pain and stiffness on Fridays and Saturdays than on other days. The general crippling is, naturally, much as before.

The following record, kept for a short period when the hip attacks were becoming less regular, serves to illustrate the periodicity:—

- May 4-6. Knee and wrist attack.
Hip attack missed.
- May 13-15. Knee and wrist attack—oedema of upper lip.
- " 16. Slight hip attack.
- May 21-23. Knee and wrist attack.
Hip attack missed.
- May 29-31. Knee and wrist attack—oedema of eyelids.

One can hardly avoid the conclusion that, in this case at any rate, the hydrarthrosis of certain of the damaged joints, and the oedema of the lips and eyelids, were part and parcel of the same morbid cycle, and that Schlesinger is right in classing intermittent hydrarthrosis among the manifestations of hydrops hypostrophos.

A case recorded by Jamieson (16) presents points of close resemblance to the above, although there is no mention of any periodic affection of joints in its course.

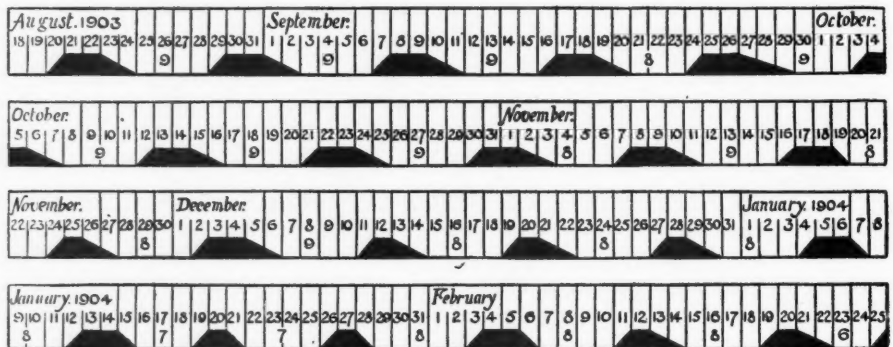
The patient was a lady, aged 60, who seven years previously began to suffer from rheumatic pains in the shoulders and nape of the neck. Later the right wrist became swollen, hot and painful; the fingers, knees, and other joints were successively involved, and many joints were, at the time of description, swollen, stiff, and distorted.

At about the same time as the onset of the articular disease the patient began to develop curious subcutaneous swellings, always upon the face and for the most part of the eyelids and lips. Their occurrence was at first irregular, but later they recurred once a week or oftener, usually on Sunday evenings, and subsided in about two days.

Between this case and those in which the periodic attacks occur in the joints alone, my case, described above, supplies a connecting link.

Case II. The patient, who was seen in consultation with Dr. C. J. Harrison, was a man, aged 43. Towards the end of December 1902 he had noticed that his right knee was slightly swollen on the inner side, and some pain was felt in it, but only at night. By the middle of January 1903 there was some general swelling of the joint, which was constantly present during the two following months, but varied in amount, sometimes within a few hours. Out of these fluctuations there gradually developed a regular periodicity of six or seven days from onset to onset, and the joint became nearly well in the intervals. The intervals gradually lengthened and by July had become extended to eight or nine days.

The patient exhibited no signs of visceral disease, and the attacks were not attended by any constitutional disturbance. He had had Jungle fever in India, and some years previously a severe attack of 'erythema', but was not subject to urticaria nor to circumscribed oedema. During the attacks the synovial capsule of the knee became distended with fluid, but comparison by means of surface thermometer showed no difference of temperature between the two knees.



Showing the intermittent hydnarthrosis of the right knee in Case II during a period of seven months. The figures immediately above the lines indicate the interval from onset to onset.

CHART. A

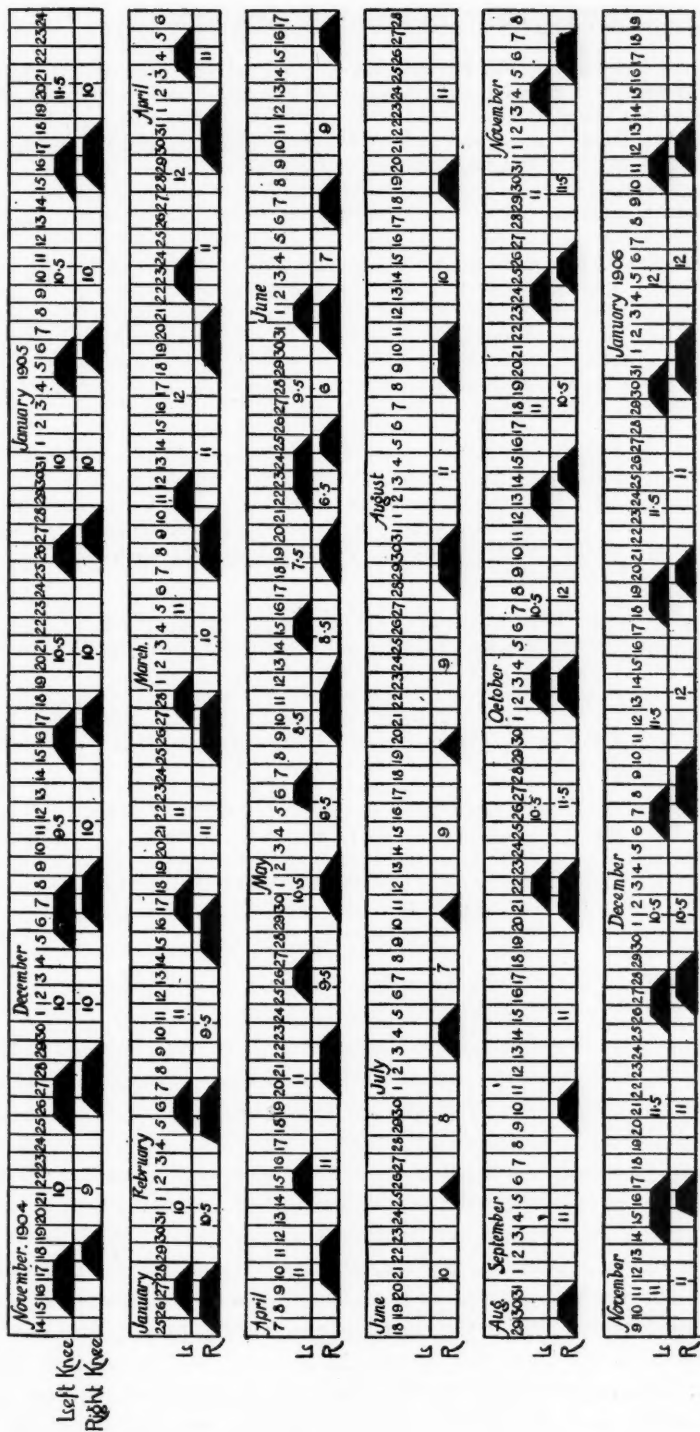
Several specimens of synovial fluid, removed by Dr. Harrison during attacks, were examined at the Lister Institute and pronounced sterile.

During the winter of 1903-1904 the attacks became much less severe, but the knee was never quite normal in the intervals. Some stiffness of the neck, shoulder, and right elbow developed, but this showed no periodicity.

In April 1904 treatment with arsenic was started, and, on the advice of the late Dr. Cromby, systematic treatment of the teeth and gums was carried out, as there was some pyorrhoea. The attacks had by then become irregular, but the improvement was much more rapid, and the patient himself had no doubt of the efficacy of arsenic in his case.

When he was last seen in July 1905 the joints gave him very little trouble, all periodicity had ceased, but when arsenic was discontinued for more than a short time he was liable to some return of stiffness. The right knee still contained a small quantity of fluid, and there was some thickening of the synovial membrane. When the joint was in movement a synovial crackle was audible with the stethoscope, but the patient could walk well and without pain.

Chart A, which has been plotted out from the accurate records kept by the patient, shows the recurrences between August 1903 and February 1904. On it



Showing the sequence of attacks in the right and left knees, in Case III, over a period of fourteen months. The figures immediately above the lines indicate the interval from onset to onset.

CHART. B

are shown the dates of onset of the attacks, of maximal swelling, and of return to nearly normal, but as no measurements are available no attempt has been made to represent the relative severity of the attacks. After this period, which was one of slow improvement, the attacks became indefinite, and the knee was the seat of more or less continuous discomfort for some months.

For convenience of reference some other unpublished cases, which illustrate points presently to be discussed, may be briefly described and numbered.

Case III is that of a man in middle age, who exhibited a crippling arthritis affecting many joints, and must be classed in the symptomatic group. Various joints were liable to periodic swelling, and the elaborate records, which the patient has kindly placed at my disposal, cover a period of no less than five years. In Chart B the attacks in both knees during a period of fourteen months are recorded, on the same principle as was adopted in Chart A. For simplicity the periodic attacks in other joints have not been charted.

Case IV is that of a young married woman, aged 23, who was in St. Bartholomew's Hospital in 1904, under the care of my colleague, Mr. H. J. Waring, who kindly allows me to quote the notes. One knee was the seat of intermittent hydrarthrosis, with a period of fourteen days from onset to onset. The case was one of the primary variety. The condition was unchanged at the time of the patient's discharge.

Case V. The patient is a girl, aged 20, who is at present under my care in St. Bartholomew's Hospital. She presents all the ordinary features of multiple rheumatoid arthritis, the onset of which dates from her fifteenth year. The left knee, and to a much less extent the right knee also, is the seat of an intermittent hydrarthrosis, with a period of seven days from onset to onset. The patient was aware that her knee was liable to become suddenly swollen, but had not recognized the periodicity of the attacks.

Cases VI and VII were remarkable from the similarity of the sequence of events in them. Both patients were men of about 30 years of age, who had suffered from gonorrhoeal rheumatism affecting the knee-joints. In both cases there followed a periodic hydrops of the knees which persisted for years, and upon this again there followed a general crippling arthritis which brought about complete incapacity, and the periodicity ceased.

In a certain number of cases the patient awakes on the morning of the day on which an attack is due with pain and stiffness of the affected joints. In some instances (e. g. *Case I*) the pain is a conspicuous symptom and may precede any swelling which is noticed by the patient, in others (e. g. *Case II*) there is no actual pain, but merely discomfort and stiffness due to hydrarthrosis. The onset of an attack may be marked by a kind of 'aura', or peculiar sensation. Thus in *Case V* a sudden sensation is experienced compared to that of 'water rushing into the joint'. However, the commencement of the attack is not always so sudden as the patient's sensations may suggest. Linberger (17) found that in one of his cases careful measurements showed that the onset was gradual, and that the interval of practical normality was in reality much shorter than it appeared to be. Weisz (18) had previously obtained a similar result, and concluded that the hydrarthrosis was, in his case, remittent rather than intermittent. His measurements indicate that the maximum of swelling was at once followed by a decline, and that, in the same way, the gradual rise began

Case V. Measurement of the two knees

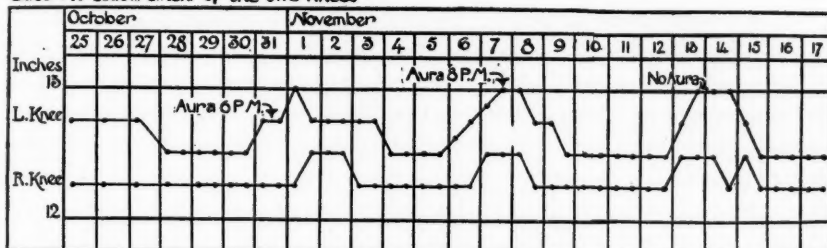


CHART C

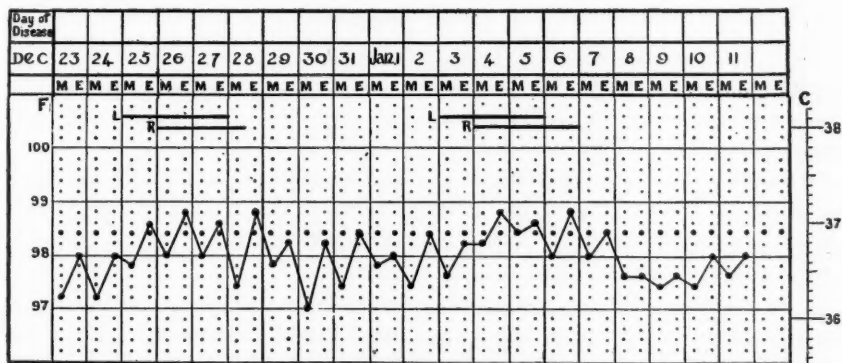


Fig. 1 Case III

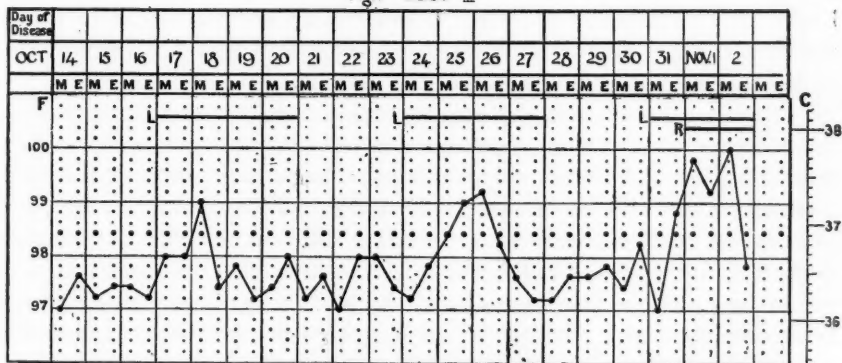


Fig. 2 Case V

The parallel lines above the temperature curve, indicate the attack in the left and right knees.

CHART. D

as soon as the minimum had been reached. When the joint was measured five times in the day well-marked minor fluctuations were demonstrated, and under such microscopic scrutiny the periodicity became to some extent obscured.

The measurements embodied in Chart C are those of the two knees in Case V. It will be noticed that the development of the swelling was more abrupt than in the cases of Weisz and Linberger, the attack being represented by a plateau rising from a level plain. However, the occurrence of the effusion preceded by some hours the sudden sensation of which the patient was conscious. Thus on Sunday, Nov. 7, the sensation of a 'rush of water' into the joint was felt at 8 p.m., but the measurement taken in the morning of that day showed that the joint was already swollen.

In some cases the affected joint feels distinctly hotter to the hand than its fellow, whereas in others (e.g. Case II) a surface thermometer fails to indicate any difference of temperature. The body temperature may be raised above normal at the time of the attacks, as is shown in Chart D, Fig. 2 (which relates to Case V), whereas in the temperature records from Case III (Chart D, Fig. 1) the normal limit is seldom overstepped, although each attack is marked by a slightly higher range than prevailed during the periods of intermission. It may be mentioned that in Case V the febrile disturbance bears no constant relation to the attack, sometimes preceding the swelling and sometimes following its development.

A series of daily blood-counts, carried out by Mr. F. A. Rose, in Case IV showed that there was a continuous slight leucocytosis (10,000 to 11,000) which was not increased during the attacks, and in Case V the number of leucocytes did not exceed the normal limits during the attacks.

In the notes of Case I and also in Chart B a point of considerable interest is brought out, namely, that when, in a complex cycle, two or more joints are involved the onset is not simultaneous in the affected joints, but that they become swollen in an ordered sequence, which may be maintained over a long period. This fact seems to supply a further argument against the dependence of the periodicity upon the life-history of a parasite.

A study of Charts A and B, and especially of the latter, also shows that the attacks of intermittent hydrarthrosis are less accurately periodic than they usually appear to be when only a few recurrences are observed. Chart A represents a period of continuous improvement, during which the duration and severity of the attacks were becoming less and less. The periods had lengthened from six or seven to eight or nine days before the chart begins, and as time goes on the intervals tend to shorten again, the last recorded being only six days. The attack beginning on Feb. 25 was the last which was sufficiently definite to be recorded, and was followed by a period of irregular swelling of the joint. In Chart B the variations are far more conspicuous. The swelling of the left knee, which in November 1904 preceded that of the right knee by twenty-four hours or more, gradually fell behind, until in May 1905 the attacks occupied an intermediate position between

those in the right knee. At the same time their duration had shortened, and they were less severe. Finally the left knee ceased to swell from June 3 to September 21. As in Chart A, this suspension of the periodic attacks was preceded by a shortening of the intervals from onset to onset. Simultaneously the recurrences in the right knee became very slight and of short duration, and the intervals between them were curtailed, in one instance to six days. When, in September, the attacks in the left knee resumed they were almost simultaneous with those in the right, but gradually regained their original position to the front.

Taken as a whole Chart B gives an impression of continual change, both in the duration of the attacks and in intervals between them; a phenomenon which may be compared with the varying severity, anticipation, and retardation of malarial attacks.

Much more abrupt changes are sometimes seen when the hydrarthrosis is resumed after an interval. The new cycle may be wholly different from the old one, and may represent no fraction or multiple thereof. Thus, in one of C. H. Moore's (19) cases the period was at one time thirty and at another nine days, and in one of Fridenberg's (20) an original cycle of twenty-one days was replaced after a pregnancy by one of twelve days.

Fridenberg's second patient, a young man whose left knee was the seat of an intermittent hydrarthrosis which followed upon an injury, stated that four years previously the attacks had recurred, on two occasions, in the right knee instead of in the left. That this statement was probably accurate is suggested by what has occasionally happened after active local treatment of an affected joint. Thus Blanc (21) applied the actual cautery to the affected knee of his patient, with the result that the attacks ceased in the joint so treated, but recurred in the other knee instead. In one of Linberger's (22) cases, also, after puncture and irrigation of the affected knee with a carbolic solution, a proceeding which was followed by cessation of the attacks, the hitherto sound knee became affected, but only after an interval of some years, and these attacks also ceased after a course of peat baths. Such occurrences clearly show that even when a single joint is for years the seat of periodic attacks of hydrarthrosis, which works some permanent damage in time, the condition cannot be regarded as a mere local affection of the joint involved, but is due to a more general process which manifests itself at a point of least resistance. The tendency to metastasis supplies a further link with circumscribed oedema, and both may well be of toxic origin, as is the more ordinary form of urticaria at least in some cases.

In gout and in acute rheumatism there is a similar tendency to metastasis of joint lesions, and although the latter malady is almost certainly infective, the character of the arthritis to which it gives rise suggests a toxic origin rather than a bacterial invasion of the joints. The sterility of the synovial fluid in every primary case of intermittent hydrarthrosis hitherto examined, including Cases II and IV of the present series, and in some secondary ones, is also consistent with such a view of its origin.

Various causes contribute to determine the incidence of intermittent hydrar-

throsis upon joints. The series of secondary or symptomatic cases bears witness to the potency of antecedent joint lesions in this connexion, and such lesions may be of gonorrhoeal origin, as in Cases VI and VII and in not a few recorded instances, or may be due to the disease commonly spoken of as rheumatoid arthritis. In primary cases the onset has not unfrequently followed upon an injury to the affected joint.

The only instance of inheritance of the tendency as yet recorded is that of a mother and daughter, described by Blanc (23), both of whom were sufferers from intermittent hydrarthrosis.

In all cases which I have met with one or both knee-joints have been affected either alone or with other articulations, and indeed only two instances are on record in which joints other than the knee were alone attacked. In this respect intermittent hydrarthrosis does not stand alone. In no less than 83 out of a series of 119 cases of gonorrhoeal arthritis the knee was involved, whereas the ankle, which is the joint next most liable, was involved in only 32 cases. Even in diseases, such as gout, in which other joints are recognized seats of election, the knee suffers in large proportions of cases.

Of concurrent conditions, pregnancy exercises the most conspicuous influence upon the course of intermittent hydrarthrosis. In almost every recorded instance in which pregnancy has intervened the articular attacks have ceased during that period, but not always throughout the period. The earliest recorded example was described by C. H. Moore in 1864, in a paper which, although it was among the earliest, remains one of the most valuable contributions to the study of the subject. His patient was free from attacks during each of a series of pregnancies from the third month to the third month of lactation, and many other examples might be quoted.

The question whether, in female cases, that essentially periodic function menstruation has any appreciable influence upon the articular troubles has naturally attracted attention. In two cases recorded by Vogt (24) and Fiedler (25) respectively, the attacks of hydrarthrosis were more severe when they happened to coincide with a menstrual period, whereas in one of Schlesinger's cases an opposite effect was noticed. Burchard (26) describes monthly attacks usually occurring at the menstrual period, and in one of Senator's cases the articular swelling appeared, as a rule, a day or two before the menses. In Case IV the alternate attacks of a fortnightly cycle tended to coincide with the periods, and Rejou (27) observed a similar coincidence of alternate attacks. On the other hand, in one of the cases described by C. H. Moore (28) the thirty-day period did not coincide with the menses.

The prognosis of intermittent hydrarthrosis is on the whole unfavourable, although the attacks may cease spontaneously or as the result of treatment. In symptomatic cases the periodic swelling is an incident, the termination of which does not very conspicuously improve the patient's state, but in primary cases recovery means very much to the sufferer.

Various local measures have been tried, such as application of the actual

cautery; incision and drainage of the affected joint; puncture and washing out with solution of mercuric chloride or carbolic acid; injection of iodine into the synovial cavity; and each can lay claim to some success in monarticular cases. However, the improvement or arrest so obtained is not always permanent, and the attacks may resume, after an interval, in the same joint, or in one previously immune. If it be true that the affection is not a local one of the joints implicated, one would hope for better results from more general treatment. Rest in bed does not restrain the attacks, which recur with as much regularity as when the patient is up and about.

Linberger obtained some improvement from passive hyperaemia, by the application of Bier's method, and the plan might well be tried in other cases. One of my patients had undergone such treatment, but stated that it had not had any beneficial effect.

Of drugs, arsenic and quinine have the best record, but both have failed in not a few cases. In three cases recorded by Professor Howard Marsh (29) the administration of arsenic appeared to have a conspicuous remedial effect, and my own experience, as far as it goes, bears this out. In Case I, recorded in this paper, the attacks became less severe shortly after the arsenical treatment was initiated, and they eventually ceased entirely. In Case II the patient was firmly convinced of the utility of the drug, although the conspicuous periodicity of the hydrarthrosis had been replaced by a period of irregular swelling before arsenic was given. However, it is not improbable that in both cases the other forms of treatment which were simultaneously employed may have contributed materially to the favourable outcome. The administration of quinine has not been attended with any success in the cases of intermittent hydrarthrosis in which I have employed that drug.

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CRITICAL REVIEW

LACTIC ACID IN METABOLISM

By J. H. RYFFEL

PART I

Identification and Estimation of Lactic Acid.

SARCOLACTIC acid was first isolated from muscle by Berzelius in 1808. Liebig in 1847 prepared calcium and zinc sarcolactates from muscle, identified the salts by analysis, and showed that the calcium salt crystallizes with four molecules of water and the zinc salt with two molecules, whilst the corresponding salts of fermentation lactic acid crystallize with five and three molecules respectively. His method of isolation consisted in evaporating the alcoholic extract of the aqueous muscle extract to a thin syrup, acidifying with dilute sulphuric acid, adding alcohol, and then ether as long as any precipitate formed, evaporating the clear ether solution, dissolving the residue in water, neutralizing with lime, filtering and evaporating to crystallization. The crystals of calcium lactate so obtained were washed with alcohol and recrystallized. The method almost universally used for the estimation of lactic acid differs from the above procedure in that, after acidifying the residue from the alcoholic extract of tissue, blood, or urine with a dilute mineral acid, the aqueous liquid is extracted many times with a relatively large volume of ether. The ether extract is then evaporated, the residue dissolved in water, heated with zinc carbonate, filtered and evaporated to dryness, the evaporation being completed in air at the room temperature so as to obtain the crystalline salt, which is then weighed. The mineral acid originally used was sulphuric acid (10), but phosphoric acid was found by Drechsel to give better results (61), especially when the alcoholic extract was first rendered alkaline with baryta and extracted with ether to remove fatty material. This method was tested by Araki (1) and found to give a pure product from muscle, and 80 per cent. yields when tried on 0.3 to 0.5 grm. of calcium lactate. In his last paper on lactic acid Araki (5), however, employed the modification of Salkowski, in which the ether extract residue is dissolved in water, warmed with lead hydroxide, filtered hot, freed from lead by hydrogen sulphide, and again extracted with ether (after acidification) for the formation of the zinc salt. The zinc salt, after having been washed with alcohol and recrystallized, is identified as zinc lactate by the characteristic shape of the crystals, and by the approximation of the percentage of zinc in the salt, dried at 110° C., to the theoretical 26.87 per cent. of zinc. The water of crystallization in

zinc sarcosylate, determined by drying the crystals at 110°C ., is 12.88 per cent., whilst that of the inactive lactate is 18.16 per cent. Attempts to apply this point for the identification of sarcosylate acid have not been very successful, so that for this purpose it is necessary to determine the specific rotation of the salt. For purified zinc dextrosylate from muscle $[\alpha]_D$ varies with the concentration from 7.55° to 6.58° (29). The rotation of the calcium and lithium salts has also been determined.

Fletcher and Hopkins found that the percentage of water in the zinc salt is liable to error from insufficient or excessive drying, so they weighed the dry salt. Moreover, finding that the extraction of lactic acid with ether is never entirely complete, whether shaking or a continuous extractor be employed, they extracted a definite number of times, using a measured quantity of aqueous liquid, phosphoric acid, and ether, so as to obtain comparable results in a series of observations.

For the identification of lactic acid Uffelmann's test is neither sensitive nor distinctive. Araki employed the decomposition to acetaldehyde and formic acid, which takes place with dilute sulphuric acid in a sealed tube at 130°C . Boas proposed to use the conversion of lactic acid to aldehyde, by distilling with dilute sulphuric acid and manganese dioxide, both as a test and for estimation. Hopkins (19) in 1906 introduced a new test, which consists in heating the material with sulphuric acid and a trace of copper sulphate in a water bath for 2 minutes, cooling and adding a few drops of a dilute alcoholic thiophene solution, when a cherry red colour is produced. This test, which depends on the formation of aldehyde from the lactic acid, is distinctive for α -hydroxy fatty acids, and is very sensitive, but cannot be applied in the presence of carbohydrate, or urinary pigment, or chromogen. Jerusalem elaborated Boas's method for quantitative purposes, but his method, which requires a preliminary ether extraction and elaborate apparatus, is not strictly quantitative, and possesses no obvious advantages over the zinc salt method.

Ryffel (50) has lately introduced a method of detection and estimation, which can be applied directly to urine free from excessive carbohydrate, and is exceedingly sensitive, giving a good reaction with 10 mg. lactic acid, whilst 3 mg. can be roughly estimated. The method consists in steam distillation of the material, to which an equal bulk of sulphuric acid has been added, by which the lactic acid yields aldehyde quantitatively. The distillate is then neutralized and redistilled. The aldehyde in the second distillate is determined colorimetrically by the use of Schiff's reagent (rosaniline hydrochloride bleached with sulphur dioxide). In applying the test to tissue or blood, the aqueous extract freed from protein by coagulation, or the evaporated alcoholic extract, may be used.

The determinations of lactic acid that follow, except those of Jerusalem and Ryffel, have all involved the use of some modification of the ether extraction and zinc salt method. In nearly every case the percentage of the base in the salt obtained was determined, and, unless otherwise specified, was not far removed from the theoretical.

Lactic Acid in normal Tissues and Fluids.

Lactic acid appears to be a normal constituent of all tissues, but except in the case of muscle the question of its formation in the process of killing the tissue has received no attention as yet.

The lactic acid obtained from brain was at first thought to be inactive (22) (43), but was afterwards shown to be dextrorotatory (42). Dextralactic acid has been obtained from liver (average 0.113 per cent.), blood, kidney, the wall of the alimentary canal, lymph glands, thymus, spleen, and thyroid (41) (42).

In blood most observers have found lactic acid. The results may be summarized as follows:—

Gaglio	Dog	Arterial blood	0.026-0.082	gm.	Zn. lactate per 100 cc.
Berlinerblau	Rabbit	"	0.102-0.157	"	lactic acid "
"	Man	Venous	0.008	"	" "
Irisawa	Dog	Arterial	0.038-0.054	"	Zn. lactate "
Morishima	Cat	"	0.024-0.040	"	" "
"	Dog	"	0.045	"	" "
"	Rabbit	"	0.093	"	" "
Ryffel (51)	Man	Venous	0.0125	"	lactic acid "

Salomon, however, found lactic acid in human venous blood only three times out of nineteen, and Jerusalem found no lactic acid in the blood of horse, calf, or pig. Probably in both cases the method was at fault.

In the normal urine of man Liebig found no lactic acid. The urine of three people, collected for two hours after taking potassium lactate equivalent to 30 grms. zinc lactate, he found highly alkaline and free from lactic acid, showing that this acid was rapidly oxidized in the body. Araki (5) obtained similar results with rabbits and dogs after injecting doses of about 4 grms. sodium lactate subcutaneously. Heuss, taking elaborate precautions to purify his product, obtained traces of a crystalline zinc salt, which contained only 15.5 per cent. of zinc from 41, 42, and 56 litres of normal urine of man. He concluded that lactic acid was not present in the urine. von Terray, extracting the urine with ether directly, obtained from man 0.1 gm. zinc salt, from dogs and rabbits about 0.2 gm., per 24 hours. This salt was crystalline, and gave Uffelmann's test, but he did not determine the percentage of zinc. It was certainly impure, so that his conclusion, that it was the inactive salt, from a determination of the water of crystallization is not reliable. Ryffel found an output of lactic acid in man of from 3.5 to 4.5 mg. per hour in the day, and 1.5 to 2.5 mg. per hour at night. As lactic acid is present in blood and in all tissues it would be surprising if there were absolutely none in normal urine. That previous observers except Terray found none may be due to the fact that evaporation with moist ether leads to the disappearance of traces of lactic acid, probably due to oxidation. Elaborate attempts to obtain a pure product lead to a further loss.

In sweat, obtained by the use of hot air, lactic acid has been found by Favre and by Ryffel (51), but not by other observers.

The Production of Lactic Acid in Muscular Activity.

Berzelius obtained much lactic acid from the muscles of hunted animals and very little from paralysed muscles. Ranke stated that fatigue and the onset of rigor were both accompanied by an increase in the lactic acid content of the muscle with a corresponding change of the reaction of the muscle from alkaline to acid. Later observers, however, obtained discordant results, especially as to the amount of lactic acid in resting muscle. For instance, Boehm obtained 0.2-0.3 per cent. of zinc lactate from resting muscle, which was killed by means of boiling water, and Marcuse, also using boiling water, showed an increase of zinc lactate produced by tetanus from an average of 0.076 per cent. in resting frog's muscle to 0.23 per cent. in fatigued muscle. On the other hand, Heffter, placing the muscle direct into alcohol, obtained 0.42 per cent. of zinc lactate in resting muscle, and argued that alcohol extracts lactic acid more completely than water. Finally, Fletcher and Hopkins, using frog's muscle, which was cooled with ice, severed rapidly from the bones and ground up at once with ice-cold alcohol, showed that under these conditions resting muscle yields only from 0.02 to 0.035 per cent. of zinc lactate, but that, if the muscle is not cooled before it is cut, or is slowly destroyed by alcohol, the result is much higher. Thus they obtained the following figures:—

Muscle injured by cutting	0.15-0.25 % zinc lactate.
" placed in alcohol at 15° C. without grinding	0.40 % " "
" fatigued	0.18-0.25 % " "
" killed by boiling water	0.08-0.13 % " "
" after production of heat rigor at 40° C.	0.38-0.54 % " "

The zinc lactate yielded in every case approximately theoretical zinc oxide.

Muscle kept in air or nitrogen showed a gradual increase of lactic acid, the rate of which depended on the temperature, until finally irritability was lost, when there was no further increase of lactic acid. If, however, the muscle was kept in oxygen there was practically no such increase at physiological temperatures, and the loss of irritability was indefinitely postponed. Moreover, the lactic acid of fatigued muscle was reduced by about half, and irritability restored in a few hours, by keeping in oxygen, but not if the muscle was injured. From these experiments it may safely be concluded that fatigue of isolated muscle and the formation of lactic acid in the muscle are parallel phenomena, and that an adequate supply of oxygen not only prevents the accumulation of lactic acid, but even enables the muscle to destroy preformed lactic acid.

In warm-blooded animals an increase of the lactic acid in the blood has been observed on tetanizing large groups of muscles. Spiro stimulated the sacral region of the cord in a dog until irritability was lost in 1½ hours, when blood from the carotid yielded 0.12 per cent. of zinc lactate. von Frey found an increase from 0.101 to 1.43 grms. of zinc lactate in the total blood, used for perfusing the hind limbs of a dog, after three hours, with tetanus lasting one hour. These experiments only confirm the statement that muscular activity can produce lactic acid, and have little bearing on the relations of lactic acid to

muscular activity in the normal animal. On this question observations have been confined to man. Spiro from 2,025 c.c. of urine passed by two men, one of whom danced for four hours, whilst the other walked for four hours, isolated 0.073 grm. of a zinc salt, which, however, did not crystallize well, and contained only 18.3 per cent. of zinc in the dry salt. Urine of the next day, 2,825 c.c., gave 0.032 grm. of zinc salt, containing 23.0 per cent. of zinc. He did not, therefore, claim to have shown the presence of lactic acid in the urine. Colasanti and Moscatelli, from 13 litres of urine passed by soldiers during and after a march of 24 km., isolated 0.48 grm. of zinc lactate, containing 26.86 per cent. of zinc. The lactate obtained was apparently quite pure, and, considering that it was obtained by the ether extraction method, cannot be accounted for by the minimal quantity of lactic acid normally present in urine. The violence of the exercise involved would, however, depend on the nature of the country traversed. Ryffel (51) found the lactic acid in urine from competitors in a 24-hours' track walking race in no case above 6.5 mg. per hour, but found relatively large quantities in that passed after violent exercise, 430 mg. after 0.36 mile, 818 mg. after 0.6 mile, running as fast as possible round a track 33 laps to the mile. The lactic acid in the blood, taken from a vein in the forearm immediately after the exercise, was also increased in one case from 12.5 mg. at rest to 70.8 mg. per 100 c.c. Excess of lactic acid disappeared from the urine in about 30 minutes after stopping, but in 45 minutes the lactic acid of the blood was not quite reduced to normal (15.9 mg. per 100 c.c.). The sudden increase of the lactic acid could scarcely fail to reduce the alkalinity of the blood, as was shown by a considerable increase in the acidity of the urine.

The older observers, arguing from their knowledge of fatigue in isolated muscle, and from their own muscular sensations, supposed that the production of lactic acid by muscle depended on its long-continued activity. In the light of Fletcher and Hopkins's results, and of the above observations on exercise in man, it is clear that this is not the case, but that the important factor is the relation between the activity of the muscles and their supply of oxygen. At rest the muscles are fully supplied with oxygen by means of the circulation. This is also practically the case with limited activity, but, when the activity is great, the oxygen supply, although increased, is not sufficient to prevent the formation of excess of lactic acid, which thus makes its way into the blood, and, if in sufficient concentration, is excreted by the kidneys. Lactic acid, however, is rapidly oxidized by the tissues, so that the return to the normal at rest is fairly rapid, occupying less than one hour after short periods of violent activity.

The Influence of Lactic Acid on Respiration and the Heart.

The injection of mineral (60) and organic (32) acids into the circulation of animals increases their respiration and reduces the amount of carbon dioxide in the blood. The respiratory centre must therefore be stimulated by a reduction of the alkalinity, or rather, as it should now be called, an increase in the acidity

of the blood. This fact is confirmed by the increase of respiration observed in diabetic coma, in which the amount of carbon dioxide in the blood is reduced and the acidity of the blood increased (7). The converse also holds good, that a decrease of the acidity of the blood by the injection of a caustic alkali depresses the respiratory centre (32). It is now generally accepted that within ordinary limits the activity of the respiratory centre is regulated by the pressure of carbon dioxide in the alveolar air and, therefore, in the blood (39) (24). Under ordinary conditions the alveolar carbon dioxide pressure in man is about 40 mm. Hg, and is remarkably constant for each individual, a rise of 2 mm. producing a definite increase of respiration (24). Carbon dioxide is chemically very inert, but is a feeble acid, so that variations of carbon dioxide pressure can apparently only produce changes in the activity of the respiratory centre by altering the acidity of the blood. Small changes of carbon dioxide would have an utterly inappreciable effect on the acidity of the blood as determined by physical methods, so that, if this view is correct, the sensitiveness of the respiratory centre to changes in the acidity of the blood must be simply marvellous.

When the hind limbs of an animal are tetanized, the carbon dioxide of the blood is reduced and that of the expired air slightly increased, whilst the oxygen of the blood is often slightly increased, so that neither accumulation of carbon dioxide nor shortage of oxygen will account for the marked increase of respiration that takes place. At the same time the acidity of the blood is increased by a substance formed in the muscles, which is presumably lactic acid (21) (34) (32). Observations on man show that, while the milder forms of muscular activity have very little effect on the alveolar carbon dioxide, violent exercise causes first a rise then a fall, which becomes more marked, and finally disappears in from half an hour to an hour after the cessation of the exercise (47) (27) (14). These facts correspond very closely with the appearance and disappearance of excess of lactic acid in the blood already described.

The changes in respiration produced by muscular exercise are, therefore, well accounted for by the theory, proposed in connexion with shortage of oxygen by Boycott and Haldane, and extended to muscular exercise by Douglas and Haldane, that the activity of the respiratory centre is regulated by the acidity of the blood, which is dependent on the amount of both carbonic acid and lactic acid present. The increased respiration of exercise has more effect in removing carbon dioxide than lactic acid, so that in course of time the carbon dioxide pressure becomes low, whilst the acidity of the blood is still high, and is only gradually reduced after the cessation of the exercise by oxidation of the lactic acid and excretion of urine containing an excess of acid.

The beneficial effect of oxygen on the respiration and pulse of exhausted athletes observed by Hill and Flack (28) may be connected with the more rapid removal of lactic acid from the circulation. In this connexion the experiment of Backman is of interest, in which he perfused the surviving rabbit's heart with Ringer's solution, to which 0.05-0.025 per cent. sodium lactate had been added, and found an increase in frequency, but decrease in force, of the heart-beat.

The application of Boycott and Haldane's theory to account for the increased respiration and reduction of alveolar carbon dioxide pressure, produced by shortage of oxygen (23) and by a reduction of atmospheric pressure (11), requires the formation of lactic acid owing to shortage of oxygen in the respiratory centre itself, or the presence of an excess of lactic acid in the blood. Lactic acid accumulates in muscle when the oxygen supply is inadequate (19). As to its formation in the intact animal the following observations are available.

Lactic Acid and Shortage of Oxygen.

Araki in a long series of experiments investigated the effect of shortage of oxygen on the formation of lactic acid in rabbits, fowls, and dogs (1) (5). The method he employed was to place the animal in a closed chamber, the air of which was kept circulating over potash by means of a pump on the Regnault principle, so as to absorb the carbon dioxide formed. The experiments were continued for four to eight hours. When the animal reached the later stages of asphyxia, as shown by collapse and slow deep respiration, more air was introduced and the experiment continued. In the earlier experiments some animals died, others required artificial respiration. The urine obtained at the end of the experiment contained lactic acid, glucose and albumen, if the animal had been well fed, but no glucose if the animal had starved for several days previously. The highest yields of zinc lactate in the urine were 1.27 grms. from a rabbit, 0.412 gm. from a dog. In the blood of a dog that died 0.36 per cent. zinc lactate was found, but very little in the urine. The urines of rabbits were neutral or acid, and the alkalinity of the blood was reduced. Unfortunately no attempt was made to determine the oxygen in the air of the chamber, so that it is only possible to conclude from the description of the symptoms of the animals that the oxygen was reduced nearly to the limit at which life becomes extinct, which is given by Stroganow as 3.5 per cent. Similar experiments using carbon monoxide poisoning instead of shortage of oxygen gave in urine 1.38 grms. of zinc lactate (rabbit), 0.205 gm. (dog); in blood 0.33 per cent. (rabbit), 0.49 per cent. (dog). The alkalinity of the blood was reduced, and the urines were acid. The lactic acid obtained with carbon monoxide and with shortage of oxygen was shown to be the dextro variety by determination of the specific rotation of its zinc salt (29). Lactic acid was also found in the urine of animals after great loss of blood (5), after cooling to 26° C. (3), after poisoning with amyl nitrite, due to the formation of methaemoglobin, and after poisoning with cocaine, morphine, curare, strychnine and veratrine, due to the resulting interference with respiration.

Araki also verified the appearance of lactic acid in the urine of dogs and rabbits poisoned with phosphorus and arsenic (4), and argued that this also was due to shortage of oxygen in the tissues produced partly by anaemia, but

still more by the impaired circulation due to fatty degeneration of the heart. This explanation, however, is scarcely adequate.

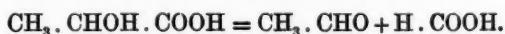
von Terray placed rabbits and dogs in a chamber ventilated with atmospheric air mixed with hydrogen. Respiration was but little altered with an atmosphere containing 10.5 per cent. oxygen, and the lactic acid in the urine scarcely increased. With 5 per cent. oxygen, however, respiration was much increased, the carbon dioxide output and lactic acid in the urine being both increased in an experiment lasting 30 minutes. With 3 per cent. of oxygen the carbon dioxide output was increased at first, but reduced later, and the lactic acid output was correspondingly greater. The zinc lactate obtained from the urines was probably impure, and no determinations of the percentage of zinc were made.

Taking the above two series of experiments together, the theory of Boycott and Haldane, that the increase of respiration in shortage of oxygen is due to the combined action of lactic acid and carbon dioxide, would appear to be amply supported. However, the reduction of oxygen in the animals' atmosphere was far greater than is required to appreciably lower the alveolar carbon dioxide of man (13 per cent. O_2). In man Ryffel (51) found no increased output of lactic acid in the urine, and practically no increase of the lactic acid in venous blood from the forearm, after an exposure of about 10 minutes to an atmosphere containing 8 per cent. oxygen, which reduced the alveolar oxygen to 4 per cent., and reduced the alveolar carbon dioxide to four-fifths of the normal, or even less. Lactic acid in the general circulation will not therefore account for the increased respiration of rapid shortage of oxygen, but it by no means follows that the lactic acid content of the blood in the jugular vein is the same as that of the general circulation. After spending four hours in atmospheric air at a pressure of 450 mm. Hg., the lactic acid in venous blood was increased from 12.5 mg. to 23.6 mg. per 100 c.c., but there was no increase in that of the urine. This reduction of atmospheric pressure was sufficient to cause a distinct fall of alveolar carbon dioxide. The increase of lactic acid in the blood, observed after 4 hours, but not appreciably after 10 minutes of much greater oxygen shortage, is of interest in two ways. It illustrates the power the kidney possesses of retaining lactic acid up to a limit not yet determined, and it suggests an explanation of the gradual lowering of alveolar carbon dioxide pressure, and the gradual development of mountain sickness, observed at high altitudes. The apparent opposition of these results to those of Araki and von Terray is explained by the fact that it is impossible to endure voluntarily shortage of oxygen as great as that which these observers employed on animals.

Origin and Fate of Lactic Acid.

In vitro lactic acid is easily formed from glucose and other carbohydrates by digesting with 20 per cent. caustic soda, the yield being as high as 50 per

cent. (45). The action of many bacteria in producing lactic acid from carbohydrates is well known. Lactic acid has also been shown to be intermediate in the transformation of glucose to alcohol by yeast (12), and to be able to take the place of carbohydrate in the bacterial production of butyric acid in some cases. On isolated muscle results have been contradictory, but Marcuse found the glycogen of frog's muscle decreased by tetanus, and Werther by survival, with an increase of lactic acid. From the Ringer's solution containing 0.1 per cent. glucose, used to perfuse a cat's heart for two hours, J. Müller obtained 0.1 grm. of zinc lactate. From the blood with which he perfused surviving dog's muscles Berlinerblau obtained 0.3 per cent. of lactic acid when glycogen was added, 0.18 per cent. without glycogen. Similarly, Embden and Almagia (15) showed that glycogen-free liver, perfused with blood poor in sugar, gave no lactic acid, while lactic acid was obtained if the liver was rich in glycogen, or if sugar, or glycogen, was added to the blood. Magnus Levy by the anaerobic aseptic autolysis of liver at 37°C. obtained lactic, formic, acetic, butyric and possibly caproic acids, hydrogen, and carbon dioxide. When the lactic acid was high the volatile acids were low, and vice versa. The lactic acid consisted partly of the inactive, partly of the dextro acid, as shown by the rotation of the zinc salt. The quantity of acids formed was in the greater number of experiments less than that which could have been formed from the glycogen and glucose which disappeared from the liver at the same time, but in some experiments it was greater. The evidence for the formation of lactic acid from carbohydrate is therefore fairly complete. Magnus Levy suggested that his experiments afford support for the view that lactic acid is intermediate in the transformation of carbohydrate to the higher fatty acids, which is known to take place in the formation in the body of fat from carbohydrate. The evolution of hydrogen and carbon dioxide and the formation of formic and acetic acids indicate that the first step in the transformation is the splitting of lactic acid into acetaldehyde and formic acid, thus:—



The formic acid then decomposes to hydrogen and carbon dioxide. Some of the aldehyde is oxidized to acetic acid, but the rest condenses and yields butyric acid and possibly caproic acid. This view has been elaborated by Leathes, and has received confirmation by Raper's synthesis of normal caproic acid from acetaldehyde.

That lactic acid is formed from carbohydrate does not preclude its formation from protein. One amino acid in protein, alanine, would yield lactic acid directly on denitrification. This Neuberg and Langstein have found to be the case on giving large quantities of alanine to rabbits, lactic acid appearing in the urine. The principal experimental evidence for the origin of lactic acid from protein has been taken to be that of Minkowski from the extirpation of the liver in geese. The urine of these animals contained ammonium lactate in greater quantity (3.5 grms. lactic acid in 12 hours) on flesh diet than on carbo-

hydrate diet (1.33 grms. of lactic acid in 12 hours). However, as the lactic acid and ammonia are present in equivalent quantities, it is quite as likely that the excretion of lactic acid is due to the formation of ammonia, which requires neutralization, as that the reverse is the case.

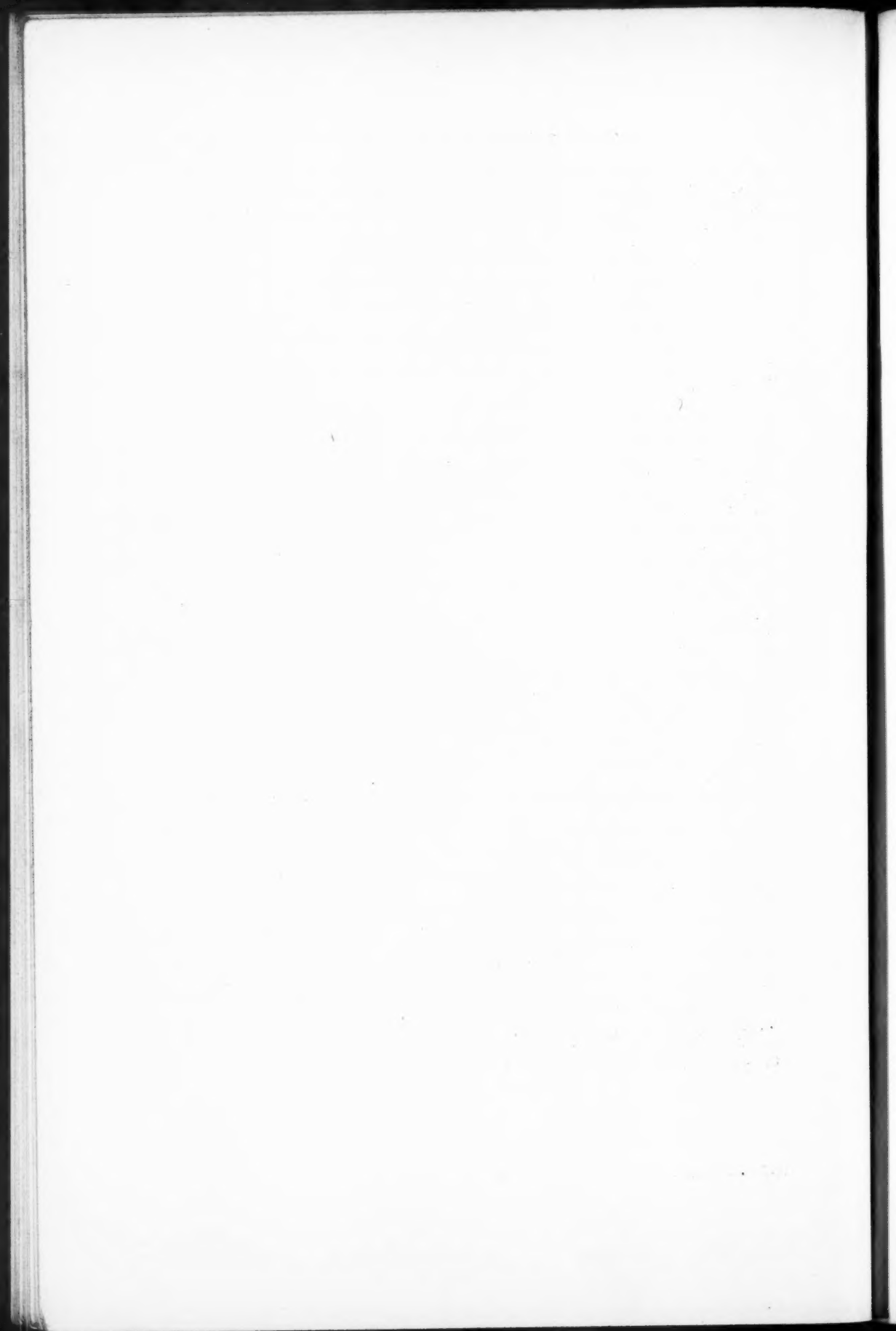
As to the further history of lactic acid, when it is not transformed into fat, Stoklasa (56) obtained from muscle and from blood by precipitation with alcohol and ether a material which had two anaerobic actions, one the conversion of glucose to lactic acid, the other that of lactic acid to alcohol and carbon dioxide, thus having similar actions to the anaerobic ferments he has since obtained from plants (57). The destruction of lactic acid, however, in muscle (19), and in the body generally, is dependent on an adequate supply of oxygen, which suggests that the first change is normally one of oxidation.

That lactic acid may be reconverted to glucose is at any rate indicated by an experiment of Embden and Salomon, in which the output of glucose by a starved depancreatized dog was very definitely increased by injecting sodium lactate. This point is further illustrated by experiments of Mandel and Lusk. They showed that phloridzin glycosuria caused the disappearance of lactic acid from the blood of a starving dog, and from the blood and urine of a dog poisoned with phosphorus. They also gave 25 grms. of sodium lactate to a starving dog with phloridzin glycosuria, and found that a diminution in the output of nitrogen followed. At the same time they attempted to calculate a formation of glucose from the lactic acid, assuming a definite $\frac{D}{N}$ ratio. As a constant $\frac{D}{N}$ ratio is by no means found even in phloridzin glycosuria, the slight glucose formation they were able to show is not very convincing. From these experiments they conclude that the excretion of lactic acid in phosphorus poisoning is not due to lack of oxygen as suggested by Araki, but to lack of ability to use lactic acid, as, when the animal is made glycosuric, the lactic acid disappears.

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THE QUESTION OF THE SIDE AFFECTED IN HEMIPLEGIA AND IN ARTERIAL LESIONS OF THE BRAIN

By ERNEST JONES

I. *Introduction.*

IN spite of occasional protests to the contrary it has for more than a century been taught that the question of the side affected by a hemiplegia is one of considerable value in the diagnosis of the nature of the affection. So far as I know, this opinion has never referred to inflammatory lesions or tumours, so that they need not here be considered. It is generally held that the fact of a hemiplegia occurring on the right side is presumptive evidence that it is due to either thrombosis or embolism, while the fact of its occurring on the left side is presumptive evidence that it is due to either cerebral haemorrhage or hysteria. The object of this communication is to examine the evidence on which these assertions are based, and to inquire into the validity of them.

The question would be unimportant, except as a matter of theoretical interest, were it not that the diagnosis of the cause of a hemiplegia is often a problem of extreme difficulty. In spite of the recent advance in our knowledge of the subject it is by no means always easy to distinguish an hysterical hemiplegia from one of organic origin, and the differential diagnosis between the three chief arterial lesions is notoriously uncertain. The great frequency with which clinical diagnoses of the latter affections are contradicted by post-mortem findings is well known to those who have had much experience of them, and indeed many competent authorities hesitate to make a definite diagnosis during life. Friedenreich(1) has recently made a careful study of the differential diagnosis between haemorrhage and softening, but made a correct diagnosis in only 89 out of 133 cases of the former condition that came to autopsy, and in 40 out of 64 cases of the latter. Not many, however, attain to this expertness in diagnosis, in which the correct diagnoses were nearly twice as numerous as the incorrect ones; as a rule the proportion is more nearly even. This uncertainty in diagnosis is peculiarly unfortunate in such exceedingly common affections, to which is due nearly a twentieth of the death-rate, because the prognosis and treatment of them are fundamentally different; it is, therefore, worth while attempting to establish any point, however slight, that would be of aid in the clinical differentiation between them. The problem has much added interest in connexion with the theory of aphasia, a matter that need not here be discussed.

A preliminary word is desirable on the scepticism necessary in approaching a problem relating to the side-incidence of any given affection. There is some obscure tendency of the medical mind to maintain of any lesion which may affect either side of the body that it affects by preference one. This is of course true of a considerable number of lesions, but certainly not of all, and it is remarkable to observe on what slight evidence writers have sometimes based their statements. It may be said that there are few such lesions of which it has not at one time or other been asserted that they occur on one side more frequently than on the other; this is so with affections of the most diverse kind, from renal calculus and ectopic gestation to Charcot's joint and herpes zoster. In view of this tendency we shall therefore be well advised not to accept any such statement unless it be supported by suitable evidence; the question of the adequacy of data needed to establish such propositions will be later considered.

When a lesion is really more prevalent on one side of the body there is usually an anatomical reason for it. The sequence of cause and effect may be either simple or complex. An illustration of the former is the greater frequency of perinephritic abscess on the right side, simply because the commonest source of the infection, the appendix, is on the right side; the tumour of intussusception and the peritonitis following perforation of a typhoid ulcer are similarly straightforward examples. In other cases the sequence is more complex, and the anatomical basis far to seek. For instance, puerperal phlegmasia alba dolens is much commoner on the left side: this is chiefly due to the greater frequency with which parametric infection takes place on the left side; the cause of this is the common localization of cervical tears on the left side; this is so because 75 per cent. of children are born with the occiput to the left, and this is probably due to the presence of the liver on the right side of the body.

A further word of caution is necessary on the subject of this anatomical basis of asymmetry. If from insufficient data the opinion is reached that a given lesion affects one side more often than the other, quite irrelevant anatomical asymmetry may be adduced in support of this opinion, and the question may be regarded as settled. The writer may go further and even assume the presence of anatomical asymmetry that does not exist. A good illustration of this occurs in the very subject under consideration. Portal (2) held that the reason why cerebral haemorrhage is commoner on the right side is that the right carotid artery is in a more direct line with the aortic stream than is the left, so that the right side of the brain is more exposed to the force of the heart-beats; while Rühle (3) held that the reason why cerebral embolism occurs more often on the left side than on the right is that the left carotid artery is in a more direct line with the aortic stream than is the right, so that fragments are more readily swept to that side. These explanations cannot both be true, but they were found so satisfactory by the authors of them as to make any further search for facts in support of the conclusions seem quite superfluous. It is clear, therefore, that we must not be tempted to relax our demands for adequate evidence merely because we are offered a specious explanation in the form of

an anatomical asymmetry. In this matter nothing can replace a satisfactory body of facts.

II. *Material.*

The question of the side affected in hemiplegia due to an arterial lesion was incidentally discussed in a previous communication (4). It is here reopened for two reasons: first, because since then I have been able very considerably to extend my data, and secondly, because I find that, in spite of great care, a number of the published cases in the collection there made were counted more than once. The difficulty of avoiding this source of error can be appreciated only by those who have undertaken similar investigations. It so frequently happens that the same case is referred to in the literature under the names of different workers that the only satisfactory way of avoiding error is to refrain from the temptingly simple procedure of adding together collections made by various writers, and to confine oneself to the actual original accounts of cases. This has involved an almost incredible amount of labour, which would have been very disproportionate to the results obtained had the present problem been more than a side-issue in the work. The actual material on which the present paper is based has been drawn from five sources:—

1. The hospital records of 154 unpublished cases of cerebral arterial lesions. These comprise all the cases of hemiplegia due to such lesions that came to autopsy in University College Hospital, London, from about 1830 to about 1900.
2. A collection from the literature of 3,697 cases of cerebral arterial lesion on which a post-mortem examination was made. Of these, 2,410 were cases of cerebral haemorrhage, 349 of thrombosis, and 626 of embolism; in 312 the nature of the lesion was not exactly stated.
3. The notes of 626 clinical cases of hemiplegia personally observed during the past six years, mostly in various London infirmaries.
4. A collection from the literature of 373 cases of hysterical hemiplegia.
5. Three published series comprising 431 cases of hemiplegia due to arterial lesions, which did not come to autopsy.

III. *Hemiplegia in General.*

It is generally stated, as remarked by Alibert (5), Baillarger (6), Weisenburg (7), and many others, that hemiplegia occurs more frequently on the right side than on the left. From this it is concluded that the left half of the brain is more liable to disease than is the right, a fact which has led to an extensive superstructure of speculation that need not here be considered. Strauss (8), on the contrary, finds that hemiplegia is more often due to disease of the right side of the brain.

We may consider separately the pathological and clinical evidence bearing

on this question. Of 3,851 cerebral arterial lesions¹ examined after death, 1,878 were situate on the right side and 1,973 on the left. In other words, of 3,851 lesions, 48.8 per cent. were right-sided, and 51.2 per cent. left-sided.

Of 1,598 cases of hemiplegia that subsequently came to autopsy, 824 were right-sided and 774 left-sided. Of 1,057 cases of hemiplegia that did not come to autopsy,² 592 were right-sided, and 465 left. If we add together the two series we see that there are 1,416 right-sided cases, and 1,239 left. In other words, of 2,655 cases of hemiplegia, 53.3 per cent. were on the right, and 46.7 per cent. on the left.

When we take into account the possible error arising from paucity of data, which can be mathematically estimated, together with the possible errors of observation and recording, it is clear that we have no right to assert, from the evidence before us, that one side of the brain is more predisposed to arterial lesions than the other, or that hemiplegia of organic origin is more likely to affect one side of the body than the other. As this evidence is by far the most extensive at present available the question must rest incompletely answered until more adequate evidence is forthcoming, but we already have enough to make us certain that any unilaterality of incidence such as is generally believed to exist must in any case be very slight, and not significant in practice.

IV. *Hysterical hemiplegia.*

So far as I know, all writers who have mentioned the question of the side affected in hysterical hemiplegia have unanimously declared that this is usually the left. This view is expressed by, for instance, Richer (13), Sollier (14), Savill (15), Roth (16), Church (17), and Brissaud (18). Strauss (19), Savill (20), Féré (21), Gowers (22), and Binswanger (23) state that the left side is affected three times as often as the right, and Whiting (24) says that 'functional hemiplegia almost always attacks the left side, perhaps four times as often as the right side'.

These opinions, however, are based not on original observations but on those made by Briquet (25) more than fifty years ago. In each of the three series of later observations collected or published by Achard (26), Bardonnet (27), and Raymond and Janet (28) the cases of right-sided hemiplegia outnumber the left-sided ones, though none of these authors observed the fact.

Our accuracy in making the diagnosis of hysterical hemiplegia has greatly increased during the past quarter of a century, so that we have not the right to rest content with conclusions based purely on observations made over fifty years

¹ The term 'arterial lesion' is here used to denote either haemorrhage or softening due to thrombosis or embolism. The cases in question are made up as follows: 202 published by Andral (9), 110 by Vulpian and Charcot (10), and the rest from the pathological material used later under the headings of the three individual lesions.

² These are made up as follows: 250 cases published by Strauss (11), 160 by Weisenburg (7), 21 by de Fleury (12), and 626 personally observed.

ago. If we submit the opinion in question to the test of more modern experience we obtain the following results: Of 79 cases published before 1880,³ 18 were right-sided and 61 left-sided. Of 294 cases published since that date,⁴ 159 were right-sided and 135 left-sided.

Thus, of the first series only 22.8 per cent. of the hemiplegias were on the right side, whereas of the second series 54.1 per cent. were. The latter series is evidently the more valid, as regards both reliability of diagnosis and extent of data. It must certainly, then, be regarded as unproven that hysterical hemiplegia affects one side more frequently than the other, and to make the question of the side of a hemiplegia serve in the differential diagnosis between hysterical and organic affections, as is generally recommended, can only tend to mislead.

V. Cerebral Haemorrhage.

It is generally assumed that cerebral haemorrhage is more apt to occur on the right side of the brain than on the left, and that consequently the succeeding hemiplegia is more often a left-sided one than a right. This, as was mentioned above, was attributed by Portal (2) to the right carotid artery being more in a line with the ascending aorta than is the left; so that, as Thevenet (38) puts it, the blood pressure is greater on the right side than on the left. It is, however, exceedingly doubtful whether there is any appreciable difference in the blood supply on the two sides, and even if there were the fact could not be allowed to replace direct evidence on the question of the side-incidence of cerebral haemorrhage. This direct evidence is remarkably slight. The assertion in question seems to have originated in a generalization of Morgagni's (39) made from the results of fifteen autopsies on cases of apoplexy. Seventy years later Gendrin (40) extended the assertion, on the basis of thirty-six autopsies, to the astonishing conclusion that cerebral haemorrhage was six times as common on the right side as on the left. Gintrac (41), in his collection of 701 cases, found that 55 per cent. of the cases of cerebral haemorrhage that were liable to cause hemiplegia occurred on the right side. Most subsequent authors, such as Hammond (42), Ranney (43), &c., have repeated at second-hand the belief that cerebral haemorrhage was more apt to occur on the right side, and only a few, such as Stelzer (44), have evinced scepticism on the point.

I have collected from the literature notes of 2,410 cases (45), which, when added to the 118 of my own series (46), make a total of 2,528 *cases of cerebral haemorrhage confirmed by post-mortem examination*. Of these 1,231 were right-sided and 1,297 left-sided, so that the above-stated opinion is not borne out by more extended investigation. This finding is confirmed by the following fact. Of these cases the side of the hemiplegia during life was noted in 876 instances;

³ 60 by Briquet (25), 8 by Mesnet (29), 7 by De Fleury (12), and 4 by Hélot (30).

⁴ 2 each by Gowers (22) and Lhermitte (31); one each by Schultze (32), Lévy-Bruhl (33), Zenner (34), and Burr (35); 9 by Voss (36), and 277 previously collected by myself (37).

438 were on the right, and 438 on the left. There is thus no reason whatever to believe that either cerebral haemorrhage or the resulting hemiplegia affects one side more frequently than the other.

VI. *Cerebral Thrombosis.*

Most of the current teaching concerning the morbid anatomy and symptomatology of cerebral thrombosis dates from the writings of the early French school, from the admirable work of Bayle, Rostan, Andral, Lallemand, and Durand-Fardel. As, however, this work was carried out before the affections of embolism and thrombosis were clearly differentiated from each other I will not quote the statistics of the cases recorded. It may be remarked, though, that by far the majority of the cases recorded by these writers were cases of spontaneous thrombosis, so that the fact that in over 500 cases published by them the incidence was approximately equal on the two sides would lead us to expect that this would be found to be so in later series.

It is only within the past half-century that the opinion has been expressed that cerebral thrombosis affects the left side of the brain more than the right; previous to this time Andral (9) had even declared that it more often affects the right side. It is to be suspected that the current teaching owes its origin to the firm belief that cerebral embolism is most often left-sided, from which it has been assumed that all clots occur more often on the left side. Leandier, writing recently in Bernheim's *System of Medicine* (47), states that cerebral thrombosis occurs 'almost always' on the left side, but most authors, including Proust (48), Vauttier (49), &c., content themselves with observing its preference for the left side, and with saying that this preference is less marked in the case of thrombosis than in the case of embolism. Laborde (50), however, found more cases on the right side, and remarked that any difference between the incidence on the two sides can only be slight, a view to which Dana (51) subscribes.

It is desirable to confine our attention to the literature since 1850, for it was only at that time that the distinction between thrombosis and embolism became recognized. From this literature I have collected the notes of 349 cases (52). These, added to my series of 23 (53), make a total of 372 cases of cerebral thrombosis confirmed by autopsy. Of these, 176 lesions were situated on the right side, and 196 on the left. The conclusion to be drawn from these figures will be considered later. Of these cases the side of the hemiplegia during life was noted in 259 instances. 149 were on the right side, and 110 on the left.

VII. *Cerebral Embolism.*

It is with cerebral embolism that writers are most certain of the predilection of the lesion for one side. Almost immediately after Virchow, sixty years ago, made clear the pathology of the condition the belief arose that it affected by preference the left side of the brain, and this belief has been held ever since.

Among the number of writers that maintain it may be mentioned Waller (54), Lancereaux (55), Meissner (56), Proust (57), Vauttier (49), Bertin (58), Lyman (59), Hirtz and Strauss (60), Hammond (61), Engel (62), Dana (63), Ormerod (64), and James Taylor (65). The value of the observation in the differential diagnosis between cerebral haemorrhage and embolism has been accentuated by Erlenmeyer (66), Hammond (67), Stelzer (44), Thevenet (38), and many others.

Nothnagel (68) says that cerebral embolism is 'far commoner' on the left side of the brain than on the right, Mackenzie (69) that it is 'almost invariably' left-sided, and Stelzer (70) that it 'rarely occurs' on the right side. Revilliod (71) states that 90 per cent. of the lesions are on the left side, and that he has only twice seen it on the other. Alexesco (72), in 1864, writes that left-sided embolism is 'excessively more frequent' than right-sided, and that only three cases of embolism of the right Sylvian artery are known; Jeannin (73), in 1894, found only nineteen cases of right-sided cerebral embolism in the literature, and goes so far as to say (74) '*Quand on dit embolie cérébrale, on entend par là embolie de la sylvienne gauche avec aphasie. L'embolie de la sylvienne droite est rare; quand on la rencontre, elle est pour ainsi dire hors de la règle, en un mot paradoxale*'.

The cases occurring on the right side have been variously accounted for. Jeannin (75) suggests that in such cases a left innominate (brachio-cephalic) artery must be present, though he admits he has never been able to find a record of such an occurrence. Cohn (76) considers that the embolus must have originated from the right innominate trunk or carotid artery. Gerhardt (77) finds that a left-sided lesion is three times as common as a right-sided one when the embolus originates in the heart valves, but not so common as a right-sided one when the embolus originates in the wall of the heart or great vessels. This conclusion was, however, based on 42 cases in which the embolus originated in the valves, and only 11 in which it originated from the heart wall. Duroziez (78) thought that a left-sided embolism is commoner than a right-sided one only when the preceding heart disease is not due to rheumatism; Strauss (79) found that embolism occurred more often on the left side in women, but not in men, and De Fleury (12) that the predilection was for the left side in normal people, but for the right side in left-handed people. The only sceptical remark on the subject I have found was one by Oppolzer (80), made in 1859, to the effect that cerebral embolism is *almost* as common on one side as on the other.

Numerous hypotheses have been put forward to account for the supposed predilection of embolism for the left side of the brain. The one that has found most favour is that already mentioned, which explains the occurrence by the direction of the blood flow from the aorta into the carotid arteries. This hypothesis was independently put forward, in 1853, by Rühle (3) and Bierck (81), though it is generally known by the name of the former writer. This view has been accepted by Cohn (82), Streuber (83), Hyrtl (84), Sunder (85), Jeannin (86), and Osler (87). Virchow (88) attributed the predilection to the fact that the left subclavian artery is not pressed on by any crossing vein, so that the flow into

the left carotid is freer than into the right; Mackenzie (69), on the other hand, attributed it to the smaller amount of blood entering the left carotid than the right. Buhl (89) saw the cause in the longer and straighter course of the left carotid, and Rosenthal (90) accepts a combination of Rühle's and Buhl's views.

Before discussing the capacity of these hypotheses to explain the fact, however, it is first desirable to determine whether the supposed fact is really one. In order to do this I have collected from the literature 626 cases (91), which, when added to my own series of 13 (53), make a total of 639 cases of cerebral embolism confirmed by autopsy. This series is about four times as large as any previous one, so that the conclusions reached should possess a correspondingly greater validity. Of the cases, in 307 the lesion was on the right side, and in 332 on the left. The side of the resulting hemiplegia was given in 353 cases, and was the right in 185, the left in 168. The conclusion to be drawn from these figures will be considered in the next section.

VIII. Summary.

Before defining the conclusions to which this study leads it is necessary to make a few remarks on the important question of adequacy of data, one that is far too much neglected in such subjects as the present one. Yet a little reflection makes it evident that an investigator who finds a lesion on the right side in 5 out of 8 cases has far less right to generalize from his observation, and maintain that the lesion in question is more liable to occur on the right side than on the left, than an investigator who finds a lesion on the right side in 5,000 out of 8,000 cases. It may next be asked, when has one the right to make such a generalization? Two matters have separately to be considered, the total numbers investigated, and the disproportion in incidence present. Plainly, if one finds a lesion ten times as often on one side as on the other, one needs fewer absolute numbers to establish the predilection of the lesion for that side than if one found a smaller disproportion between the two; conversely, a small disproportion gains in significance as the extent of data increases. Thanks to the modern mathematical theory of probability we are now in a position to make exact statements on such matters, and to say that when, in a given series of cases, the disproportion between the two sides exceeds a certain amount, then it cannot be accounted for merely by chance, but that the observation needs some other explanation. For example, if out of 100 cases the lesion is on the right side in 80 and on the left in 20, it can be definitely asserted that however great a number of similar cases may be investigated the right-sided lesions will always exceed left-sided ones, though, of course, not necessarily to the same extent; some other explanation than that of chance must be invoked, and this may be (1) that such right-sided lesions are in fact more frequent than left-sided ones, or (2) that right-sided ones were consciously or unconsciously selected in preference to left-sided ones in the series in question. There are thus always three possible explanations of a disproportionate incidence of lesions on one

side: (1) paucity of data, in which the disproportion is due only to chance, (2) selection of material in favour of one side, (3) real predilection of the lesion for that side. Before we are justified in accepting the third explanation as the true one, we are obliged first to exclude the possibility of the other two.

We may now restate the observations collected and then discuss them in the light of the considerations just brought forward.

Cerebral Arterial Lesions.

	Total.	Right.	Left.	Percentage on Right.	Percentage on Left.
Haemorrhage	2,528	1,231	1,297	48.7	51.3
Thrombosis	372	176	196	47.3	52.7
Embolism	639	307	332	48.0	52.0
Nature not stated	312	164	148	52.5	47.5
Total	3,851	1,878	1,973	48.8	51.2

Hemiplegia due to Cerebral Arterial Lesion.

	Total.	Right.	Left.	Percentage on Right.	Percentage on Left.
Lesion defined at autopsy { Haemorrhage	876	438	438	50.0	50.0
{ Thrombosis	259	149	110	57.5	42.5
{ Embolism	353	185	168	52.4	47.6
Cases with nature not defined	1,167	644	523	55.2	44.8
Total	2,655	1,416	1,239	53.3	46.7

Hysterical Hemiplegia.

	Total.	Right.	Left.	Percentage on Right.	Percentage on Left.
Before 1880	79	18	61	22.8	77.2
Since 1880	294	159	135	54.1	45.9
Total	373	177	196	47.5	52.5

Of the four affections under discussion that of thrombosis most gives rise in these figures to the supposition of its possessing a predilection for one side rather than the other, and particularly in its clinical aspects. Let us, therefore, consider the latter observation, in which out of 259 hemiplegias 149 (i.e. 57.5 per cent.) were right-sided. Now all that can legitimately be concluded from this fact is, that, if a great number of *similar* series were investigated, the number of right-sided hemiplegias would always be something between 126 and 172, and no one can at all predict to which number between these two extremes it would most approximate. It might in reality be below 129.5, i.e. below 50 per cent. It can be shown mathematically that when 259 instances are taken at random of a condition that has no predilection at all for one side rather than the other, the number of them that will belong to a given side will lie anywhere between 107 and 152, and may as well be near one of these extremes as near the other. If, therefore, in such a series it were observed that more than 152 cases were

right-sided then some explanation other than that of chance would have to be sought; some selecting agent must have been present.

As it is, no further explanation whatever of the figures is called for, a conclusion that is supported by the larger series of autopsies on cases of the same nature in which the disproportion is notably less. It is, therefore, not necessary to go further into the matter and inquire, for instance, into the selection of the series that must have occurred in regard to both thrombosis and embolism by the publication of so many cases of right-sided hemiplegia on account of the aphasia that is apt to accompany such conditions.

What has been said in relation to the statistics of thrombosis applies even more obviously to those of the other affections, so that it is unnecessary to discuss these further.

IX. *Conclusions.*

5,281 cases of cerebral haemorrhage, thrombosis and embolism, and hysterical hemiplegia have here been studied from the point of view of the side of the lesion or of the hemiplegia; in 3,539 of these the nature of the lesion was definitely determined by post-mortem examination.

With none of these conditions was any evidence obtained to indicate that either the lesion or the hemiplegia is more apt to affect one side rather than the other. The general teaching to the contrary is not founded on any critical evidence.

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| <i>A. J.</i> , The American Journal of the Medical Sciences. | <i>D. M. W.</i> , Deutsche medizinische Wochenschrift. |
| <i>A. de N.</i> , Archives de Neurologie. | <i>Ed. M. J.</i> , Edinburgh Medical Journal. |
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| <i>B. K. W.</i> , Berliner klinische Wochenschrift. | <i>G. H.</i> , Gazette des Hôpitaux. |
| <i>B. M. J.</i> , British Medical Journal. | <i>I. D.</i> , Inaugural Dissertation. |
| <i>B. S. A.</i> , Bulletin de la Société anatomique de Paris. | <i>J. N. M. D.</i> , Journal of Nervous and Mental Disease. |
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| <i>C. R. A. S.</i> , Comptes-rendus de l'Académie des Sciences. | <i>M. R.</i> , Medical Record. |
| <i>C. S.</i> , Transactions of the Clinical Society of London. | <i>M. T. G.</i> , Medical Times and Gazette. |
| <i>Dublin J.</i> , Dublin Journal of the Medical Sciences. | <i>N. C.</i> , Neurologisches Centralblatt. |
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ON ACUTE PYELITIS DUE TO BACILLUS COLI AS IT OCCURS IN INFANCY

By JOHN THOMSON

WITH PATHOLOGICAL REPORTS ON TWO FATAL CASES OF PYELO-NEPHRITIS

By STUART McDONALD

With Plates 4 and 5

WHEN a child's urinary tract is invaded by *Bacillus coli* we may, clinically speaking, have one of four things:—

1. *Simple bacilluria*. Acid urine, with perhaps an offensive smell, containing *Bacillus coli* in large amount but no pus: no subjective symptoms, except enuresis or an increased frequency of micturition.

2. *Cystitis*. Numerous pus cells and *Bacillus coli* in acid urine: increased frequency of micturition with, sometimes, a degree of dysuria (which is generally very slight); little or no rise of temperature: and no general illness or distress.

3. *Pyelitis*. A similar state of the urine: with a high remittent type of temperature, which is often ushered in by shivering or rigors: and, in most cases, serious general disturbance and great distress.

4. *Suppurative nephritis*. A similar condition of the urine, but with more albumin and some tube-casts: severe general symptoms, with more cachexia than in uncomplicated pyelitis: resulting in extreme exhaustion, and, if the kidney affection is extensive, in death.

In cases of pyelitis there may, or may not, be signs of cystitis also; and in certain cases of cystitis with severe symptoms it is probable that the pelvis is involved to some degree. The instances of suppurative nephritis I have seen appeared to be secondary to pyelitis; but it seems quite possible that this condition may sometimes arise primarily.

Acute pyelitis from *Bacillus coli* may occur in men, in women (especially during pregnancy), in older children, and in infants of both sexes. In this paper I wish to speak of the disease as it occurs in children under two years; and what I have to say is based on the study of twenty-five cases, met with in hospital and private practice during the last fifteen years. These include eight cases previously published. I shall deal (1) shortly, with the causation (bacteriology, course of infection, and predisposing influences); (2) with the clinical features and diagnosis; (3) with the treatment, and its results; (4) with

the prognosis; and (5) with the spread of the infection to the kidney as a cause of death in fatal cases.

Bacteriology. The infecting agent in this disease is the *Bacillus coli*, and, presumably, it is derived from the patient's own bowel. In all of my cases which were examined bacteriologically a bacillus of the coli group was found, and in most of them the organism was a typical *Bacillus coli communis* in all its reactions. In some of them, however, as in Case XX, this was not the case.

Dr. James Ritchie kindly investigated the bacteriology of Cases XIX and XX, which were in the hospital at the same time. He reported that 'the catheter specimens taken from Case XIX on Nov. 7, 1907, gave a pure culture of a bacillus which showed all the morphological and cultural characters of *Bacillus coli communis*. This organism was clumped in half an hour with the serum of Case XIX, in dilution of 1-45, but not at all with that of Case XX. Twelve days later, no culture could be obtained from the urine. When the child's urinary affection recurred (Jan. 14, 1908), the same organism was again obtained from a catheter specimen. On all the occasions on which the urine was examined, no organisms except the *Bacillus coli* were obtained by aerobic methods.

'The examination of a catheter specimen from Case XX, also obtained on Nov. 7, 1907, and examined by the same methods, yielded the following results. On McConkey's lactose plates a Gram-negative bacillus was grown which differed from the typical *Bacillus coli* in that it gave no acid or clot in litmus milk; and, while it gave acid and gas in glucose bouillon, and indol in peptone water, there was no development of acid and gas in lactose bouillon. This organism gave a nearly complete agglutination reaction with the serum of Case XX in half an hour, in a dilution of 1-35. It gave a similar reaction, in the same dilution, with the serum of Case XIX. The serum of Case XX gave no reaction with an ordinary laboratory culture of *Bacillus coli*. The technique of the taking of the catheter specimens of Cases XIX and XX was controlled by the examination of specimens taken from the bladders of several female children who were being treated in the hospital for other diseases. In all of these the urine was sterile.'

Course of the infection. The question whether, in any particular case, the bacilli have passed from the bowel to the pelvis of the kidney directly through the tissues or have been carried there by the blood-stream, or whether they have spread upwards from the outside by way of the urethra, bladder, and ureters, is difficult to answer. Any of the three routes, or some combination of them, may be taken. It seems certain, however, that the organisms in the cases we are dealing with most frequently ascend along the urethra. It is difficult to see how else we can explain the fact that the very large majority of the patients are girls. When we find one side much more affected than the other, as in Case XXV, this certainly seems to be in favour of the view that the disease has spread upwards from below. It may, however, be doubted whether the ascending organisms always pass upwards inside the lumen of the ureters, or whether they may not also go outside them in the deeper tissues.

In connexion with Wreden's observation that cystitis is apt to occur in male rabbits when the mucous membrane of the bowel has been injured; it is interesting to note that there was a history of marked constipation (which had often been treated by soap or glycerine suppositories) in twelve cases; and that in nine of these, blood had been noticed in the stools. In one case, also, the symptoms of pyelitis had occurred a fortnight after circumcision. Morse has recorded two cases following this operation.

Predisposing influences. A very important point in the etiology of this condition is the question as to the precise nature of the local or general predisposing causes which have so weakened the natural defences of the urinary tract as to make it liable to be invaded by its normal neighbour the *Bacillus coli*. Probably the weakening influence may sometimes be of the nature of a chill; possibly some chemical change in the urine may have occurred. The histories of my cases do not throw any very helpful light on the subject, but many of the patients had evidently been weakened by previous disease. Thus, three certainly, and probably five, were suffering at the time from infantile scurvy; three at least from severe dyspepsia and diarrhoea, and others from a lesser degree of indigestion; one had profound anaemia (as occurred also in a very similar case of pyelo-nephritis described by H. C. Carpenter): and one had otitis media. In three cases the symptoms set in about a month after an influenzal attack. Eleven of the patients were said by their mothers to have been in good health when the symptoms set in.

Clinical features.

Age. The disease is commoner before than after two years old; and its manifestations are generally (though not always) more characteristic and severe in young babies than they are in older children. The ages of my patients varied from one to twenty-one months, the majority of the children being between three and nine months. (See Summary of Clinical Features.)

Sex. The patients were mostly girls (twenty-one out of twenty-five). In the cases hitherto published the proportion of girls has been even greater than this.

Feeding. The children were usually (twenty-one) bottle-fed; but in two cases they were on the breast, and in other two on both breast and bottle.

Hygienic surroundings. In most of the cases these were quite satisfactory. Only one of them occurred in very poor circumstances; and fully one-half of the remainder were in children of very well-to-do people.

Season of the year. Cases occurred in every month of the year except August, during which month I am usually out of town.

Symptoms. These cases are characterized by the extreme severity of their general symptoms and the very trivial and equivocal nature of the local manifestations. The children are obviously very ill, and yet there is nothing distinctive to be found, beyond a little pus in the urine.

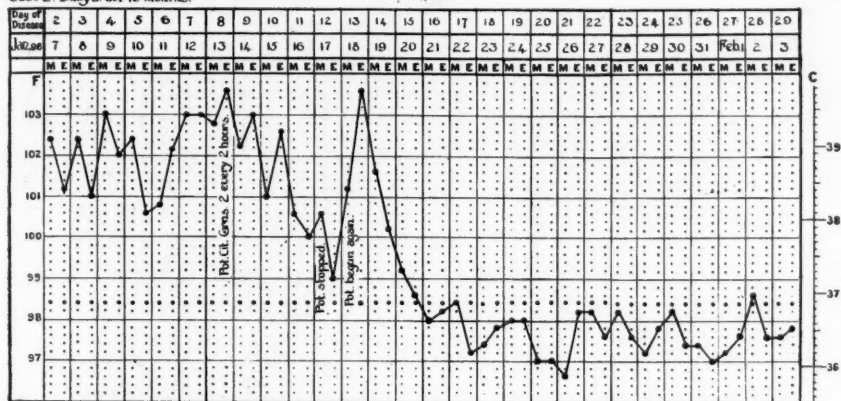
SUMMARY OF CLINICAL FEATURES

No.	Name.	Sex.	Age in Months.	Date.	Habitual Constipation.	Blood in Motions.	Previous Diarrhoea.	Other Predisposing Conditions.	Convulsions, Rigors, Shiverings, and Faint Turns.	Vomiting.	Dysuria and Frequent Micturition.	Subsequent History.
1	Baby M.	F	20	June '95	x	x	x	Scurvy, Rickets	?	x	?	Fairly good health
2	Baby J.	F	10	Jan. '98	x	x	x	Scurvy	?	x	x	Good health
3	Baby P.	F	10	April '98	x	?	x	Severe Dyspepsia	Rigors	?	?	Good health
4	Baby G.	F	12	July '00	x	x	x		0	x	x	Died within a year, probably from tuberculosis
5	E. R.	F	14	May '01	x	0	x	Influenza 1 month before	Slight rigor	0	0	Good health
6	Baby W.	F	14	April '01	?	0	x		0	x	x	Fairly good health
7	Baby H.	F	7½	July '01	x	x	x	Influenza 1 month before	Rigors	0	0	Good health
8	Amy S.	F	18	Oct. '01	x	x	x	Debility, Dyspepsia	Rigors	?	x	Good health
9	Baby Sk.	F	12	Sept. '03	x	x	x		Slight rigor	?	x	Lost sight of
10	Margt. C.	F	20	May '04	x	x	x		Shivered once, 'queer nervous turns'	0	0	Good health
11	Mary T.	F	12	March '05	x	0	x	Rickets, Influenza	'One bad shivering fit'	?	x	Good health
12	Baby S.	F	6	May '05	0	0	x	Circumcision 14 days before	Very severe rigors	?	x	Good health
13	Baby D.	M	2½	March '06	0	0	x		0	0	0	Good health
14	Margt. D.	F	6	June '06	0	0	0	Otitis	A severe rigor	0	?	Lost sight of
15	Alice P.	F	12½	Sept. '06	0	0	0		0	x	0	Died, probably from pyelo-nephritis
16	Isabel T.	F	9	Oct. '06	?	?	x	?	One rigor	x	?	Good health
17	Mary C.	F	9	June '07	?	?	?	? Scurvy	Rigor	?	?	Good health
18	John B.	M	1	Oct. '07	0	0	0	Phimosis	0	x	x	Died some months later of broncho-pneumonia
19	Dorothy L.	F	5	Nov. '07	?	0	x	Scurvy, Rickets	Rigor	x	x	Relapsed two months later: recovered rapidly, since well
20	Daisy C.	F	9	Nov. '07	x	x	0	Rickets	Rigor	x	0	Good health
21	Florence O.	F	19	Sept. '08	0	0	0		Convulsions, slight rigors, and faint turns	x	x	Good health
22	Isabel S.	F	5½	Feb. '09	x	x	x	? Scurvy	0	0	x	Good health
23	Ernest H.	M	7	Dec. '08	0	0	0		0	0	0	Died from pyelo-nephritis
24	Baby C.	F	4½	March '09	0	0	x	Tuberculosis	Rigors	x	x	Died some weeks later from abdominal tuberculosis
25	James T.	M	3	March '09	0	0	0	Extreme Anaemia	Faint turns with rigidity	x	0	Died of pyelo-nephritis and broncho-pneumonia

tis and broncho- pneumonia

CHART 1

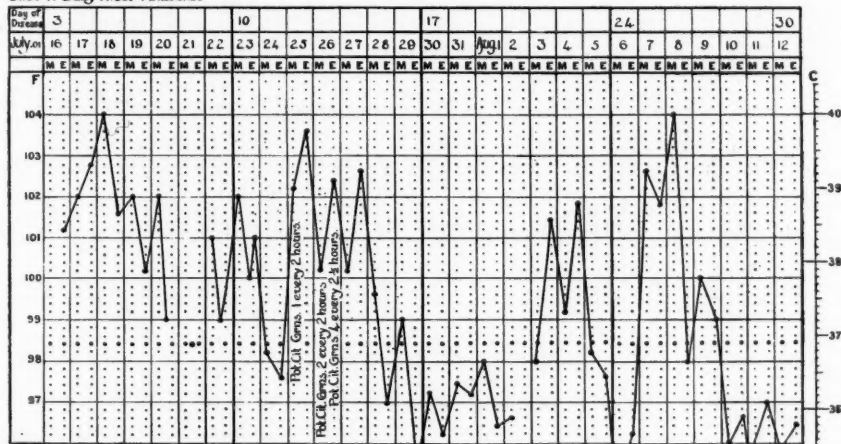
Case 2. Baby J. aet 10 months.



Steady recovery on small doses of citrate of potash

CHART 2.

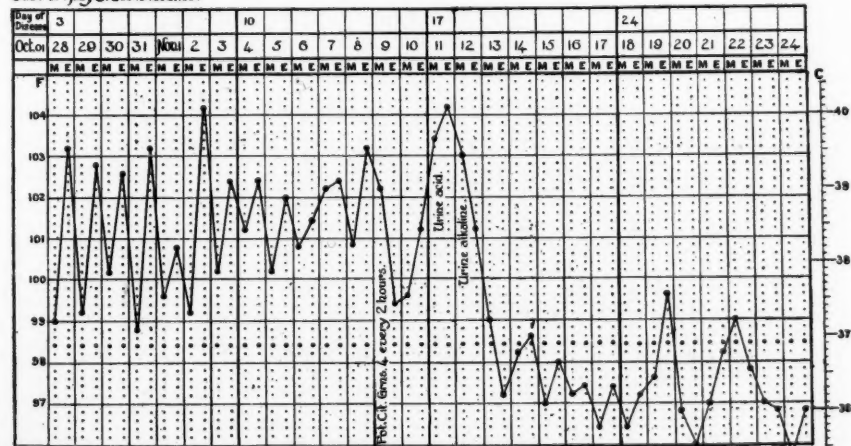
Case 7. Baby H. aet 7 months.



Rapid improvement on citrate of potash followed by a week of pyrexia before ultimate recovery

CHART 3.

Case 8. Amy S. aet 18 months.



Rapid and satisfactory recovery under steady administration of citrate of potash. Secondary rise of temperature very slight.

CHART 4.

Case 10. Margt. C. aet 20 months.

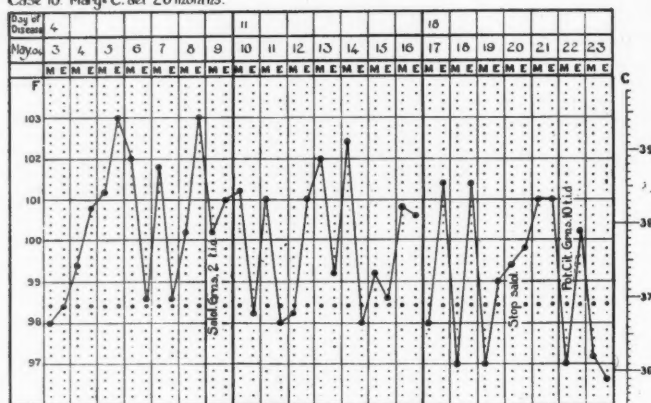
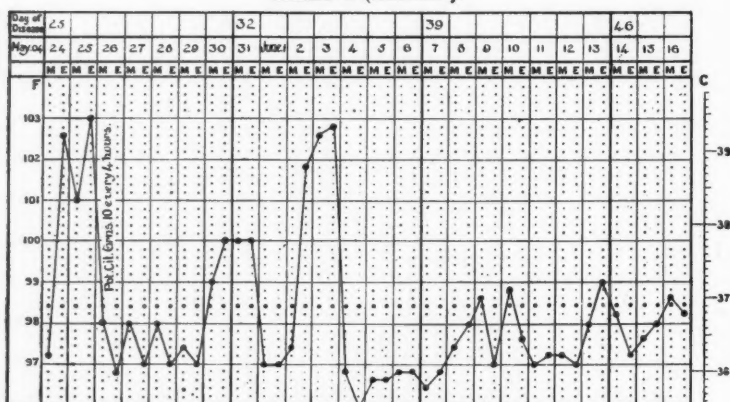


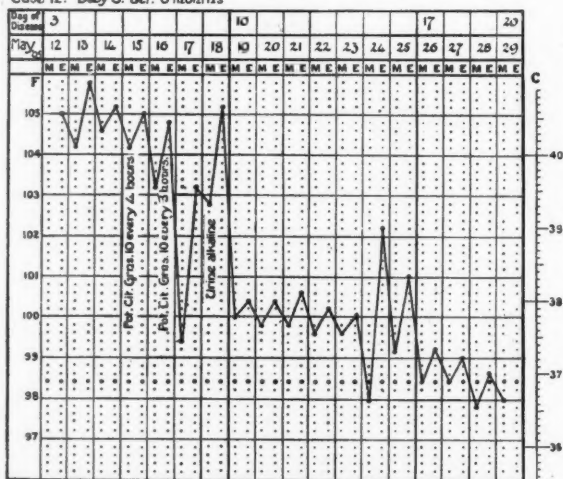
CHART 4 (continued).



Persistent pyrexia until commencement of alkali treatment on 24th, thereafter rapid recovery with considerable secondary pyrexia

CHART 5.

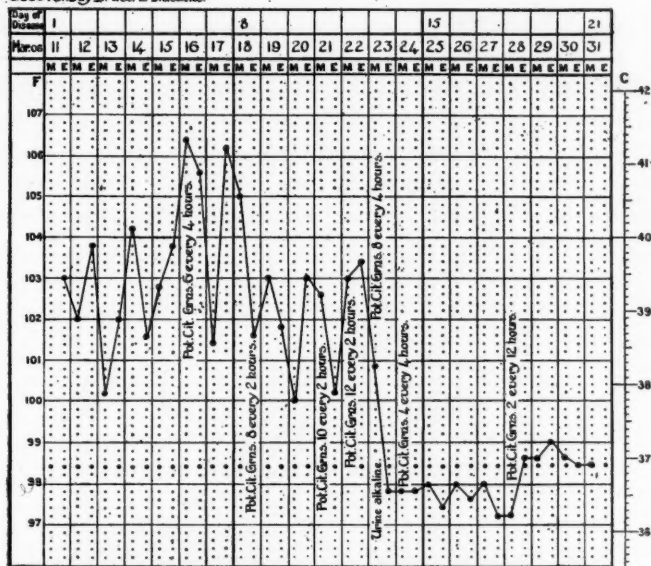
Case 12. Baby S. aet 6 months



Typical severe case which yielded rapidly to citrate of potash

CHART 6.

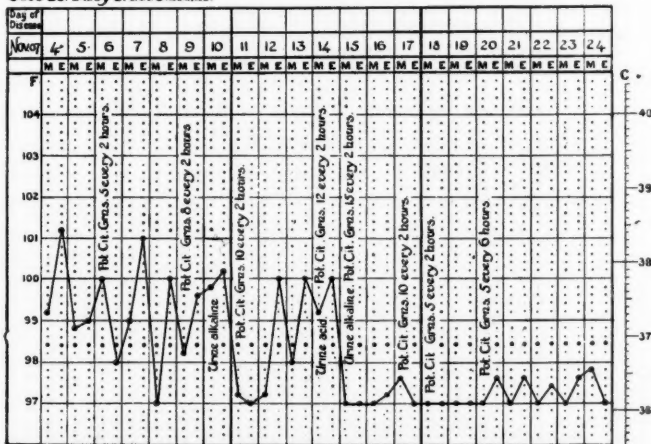
Case 13. Boy D. aet. 2 1/2 months.



Severe case which needed unusually large doses of citrate of potash to neutralise the acidity of the urine, probably owing partly to the presence of diarrhoea. Rapid recovery when the urine at last became alkaline.

CHART 7.

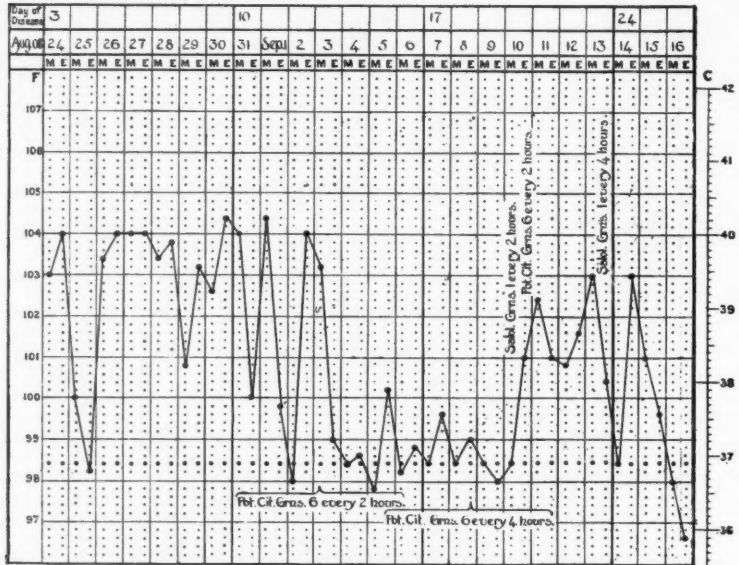
Case 20. Daisy C. aet. 9 months.



Case with moderate pyrexia which required unusually large doses of citrate of potash to render the urine alkaline, and to keep it so. There was no diarrhoea.

CHART 8.

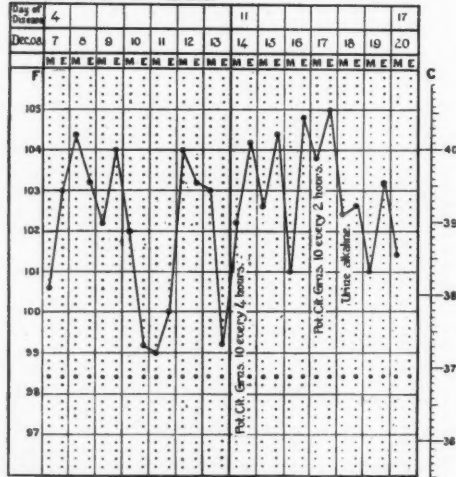
Case 21. Florence O. aet. 10 months.



Typical severe case showing rapid improvement; and complete recovery after a sharp recurrence of pyrexia for a week.

CHART 9.

Case 23. Ernest H. aet. 7 months.



Fatal pyelonephritis. Shows persistence of pyrexia after alkalinization of the urine.

The onset of the illness was usually said to have been sudden; but, on making inquiries, it was sometimes possible to find out that there had been an increased frequency of micturition or an offensive smell of the urine for some days or weeks before the acute symptoms began.

Pyrexia. The temperature ran up rapidly, often reaching 104° or higher, and assumed a remittent type which was often like that of enteric (see Charts). If the case was untreated, or ineffectively treated, this character of the temperature might be maintained for many weeks, or there might be repeated severe relapses with intervals of a few days of normal temperature. Under proper treatment the temperature fell by crisis in a few days. It showed a tendency in many cases, as we shall see later, to rise again for a short time after a few days; but with this exception it almost always remained normal, and the recovery was permanent. In rare instances there was a relapse some weeks or months later.

Rigors, convulsions, and faint turns. Along with the sudden rise of the temperature there was, in a considerable proportion of cases (15), either a noticeable shiver (5) or a definite, well-marked rigor (10). In two of the cases the occurrence of a distinct convulsion was described. The description which was given of the seizure in these cases, however, suggested that it probably began as a rigor and ended in loss of consciousness—passing into an eclamptic attack, just as the paroxysms of laryngismus and those of whooping-cough often do. In two of the cases the children had suffered from recurrent attacks of faintness with general rigidity, but with no shivering.

It is noticeable that in none of the four cases in which the patient was a boy was any shivering or rigor observed: and I do not remember to have seen any account of a boy with this disease having had a rigor. Whether the rarity of an ascending infection in boys has anything to do with this seems possibly worth considering.

The frequency of rigors in these cases is interesting, and at times their occurrence may help to draw attention to the diagnosis. One occasionally sees babies suffering from meningitis, pneumonia, and other inflammatory diseases who are said to have shivered at the onset of the fever. I have never, however, seen a baby under two years who was described as having had a regular rigor and who had not pus in the urine.

General disturbance and distress. These were very marked when the temperature was high; and the children were drowsy and often delirious, they often squinted, their respiration was quickened, and they usually vomited. They were also restless, very miserable, and tender to touch all over. In many, though not in all cases, there was an utter distaste for food.

The blood showed some degree of leucocytosis (16,000-26,000) in all cases in which it was examined, except in one (Case XXV) in which the patient was dying in a state of collapse, with the kidney affected and with bronchopneumonia. In Case XXIII, in which the kidney was the seat of abscesses, the leucocyte count was 36,000.

The *local symptoms* were either very slight or seemed to be quite absent. Colicky pains were sometimes described, sometimes frequent micturition or slight dysuria, and occasionally there was tenderness over one or other loin. The exact localization of tenderness is, however, exceedingly difficult owing to the child's general sensitiveness. Vulvitis and vaginitis were never observed.

The *urine*. The characteristic features of the urine were that it contained a considerable number of pus cells and clumps of *Bacillus coli*, and was very distinctly acid. A few red blood corpuscles were sometimes found also, and occasionally a hyaline or granular cast. There was a trace of albumin, accounted for by the amount of pus present. Generally the urine had no offensive odour, but often there was a history of there having been a bad smell at the time the symptoms began, or some days before. It does not seem possible, by the examination of the urine alone, to distinguish pyelitis from cystitis.

Three facts which are important from a clinical point of view require mention here :—

1. At the time the temperature first rises, no pus is often (perhaps ever) to be found in the urine. It always appears, however, within a few days.

2. The pus may, at a later stage, disappear from the urine for a day or two, and then reappear. This is probably due to one ureter being mainly affected at the time, and to its having become temporarily blocked while the other remains patent. (Göppert.)

3. Although the urine is acid on passing, it tends rapidly to become alkaline on standing. One is apt, therefore, to be misled if one tests the reaction of urine which is not freshly passed.

Diagnosis. This rests on two things: (1) the presence of pus in the urine, along with the severe general symptoms already described; and (2) the absence of any ascertainable organic disease of other parts sufficient to account for these severe symptoms. This last is important. I have, for example, more than once seen cases of tuberculous meningitis diagnosed as acute pyelitis because of the presence of pyuria, when the pus in the urine was really due to the occurrence of a secondary, terminal cystitis. On the other hand, acute pyelitis is often mistaken for meningitis, owing to the severe nervous and general symptoms which it occasions, and because it is not recognized that so severe an affection of the urinary tract may be indicated by so slight a symptom as a little pus in the urine.

Treatment. In this the main indications are two. The first of these is to ensure a copious discharge of urine, which is effected by giving fluids freely, by the mouth if possible, and, if not, by the rectum (saline enemata).

The other, which is the most important, is to render the urine alkaline on passing, and to keep it so for a time. This is done by administering citrate of potash or some other alkaline remedy. The dose of the citrate which is required varies greatly in different cases. The smallest amount that I have seen effectual is 24 grs. in the day (Case II). I usually begin with 48–60 grs., and increase to 120, 150, or even 180 grs. in the twenty-four hours, if the urine

remains acid. The time it takes to make the urine neutral or alkaline also varies according to the doses of the medicine given and the severity of the case. The state of the bowels may have something to do with this: because, if the citrate sets up profuse diarrhoea, its effect on the urinary reaction is, of course, weakened (Case XIII). Generally the urine becomes alkaline in four or five days; occasionally, in between one and three; and sometimes it takes six or seven days, but never more.

The best idea of the effect of the alkaline treatment on the cases can be obtained by looking at the temperature charts, because, when the temperature falls, the other symptoms always improve; and any recurrence of the other manifestations of the disease (such as increase of the pus, of the acidity of the urine, or of the general distress) is accompanied by a rise of temperature.

On studying the charts and records of other published cases as well as my own, certain generalizations seem justified:—

1. When an alkali is not given, or is given in insufficient doses, the case may recover; but the course is apt to be very protracted (Case X). The risk of relapses and of extension of the disease to the kidney under these circumstances is probably considerable.

2. If the kidneys have become seriously affected by the time the treatment is begun, the alkali does not reduce the temperature, and neither it nor anything else seems to do any good (Case XXIII).

3. When, in an uncomplicated case of acute pyelitis, an alkali has been given in sufficient amount to render the urine alkaline on passing, the temperature always falls to normal or nearly normal within a day or two at most. Along with this the general symptoms improve greatly, and the pus disappears from the urine, though a pure culture of *Bacillus coli* may sometimes be got from it for weeks or even months after.

4. It is interesting to notice that, even if the alkali is pushed, there is generally a strong tendency for the urine to become acid again a few (3-7) days later, and with this, as already indicated, the temperature rises and the other symptoms return. In some cases this secondary rise of temperature is severe (Cases VII, X, and XXI); in others it is slight (Cases VIII and XII). In others again, especially in those in which very large doses of alkali have been given (Cases II, XIII, and XIX), it does not occur at all.

5. I have never had any case of acute pyelitis in a young infant in which other organisms were found along with the *Bacillus coli*. In cases of such mixed infection in older children, however, the use of citrate of potash in large doses has never seemed to do good, and usually has appeared to be positively harmful.

In addition to the free administration of fluids and the use of alkalis, it is advisable to keep the bowels open; and, for this, phosphate of soda is probably the best drug to use (R. Hutchison), because it tends to render the urine alkaline. An occasional dose of calomel is also beneficial.

Antiseptics of various kinds, especially salol and urotropin, have been often recommended in the treatment of pyelitis. When given apart from the alkaline

treatment their action is unreliable and disappointing; and the symptoms tend to relapse repeatedly. Given in addition, I have several times thought that their use was followed by some improvement. Generally, however, in my experience, the improvement under citrate of potash, if it was given in sufficient doses, has been so steady and satisfactory that nothing else has been called for. For the same reason I have had practically no experience of bacteriotherapy in this disease. It has been tried by various observers with varying but often not very satisfactory results.

Prognosis. Of my twenty-five cases, twenty-one recovered, three died from the disease spreading to the kidney, and one of abdominal tuberculosis. Two of the patients who recovered from the urinary condition died some time later, one from acute broncho-pneumonia and the other (in England) from what was probably tuberculosis. Of the remaining nineteen, two have been lost sight of; the others are all well, and, with one exception (Case XIX), none of them has had any further urinary symptoms. The eldest of the patients is now 16, and two others over 12 years old. Of the three who died, two were examined post mortem, and were found to have a *Bacillus coli* affection of one or both kidneys (*v. infra*). One of these (Case XXIII) died from the kidney affection only, the other (Case XXV) from an intercurrent broncho-pneumonia. In the third case (Case XV) a spread to the kidney probably existed as in the other two cases. In it the alkaline treatment failed to affect the symptoms, and the child took convulsions and died. There was no post-mortem examination.

Extension of the infection to the kidney. Cases of pyelo-nephritis from *Bacillus coli* have been frequently published (e.g. by Baginsky, Trumpp, H. C. Carpenter, Abt, Rach and v. Reuss, and J. P. West); but the risk of a fatal extension from the pelvis to the kidneys occurring, especially when the treatment has not been sufficiently prompt and thorough, seems perhaps to be worthy of more attention than it has received. I therefore conclude with an account of the symptoms and post-mortem appearances of two cases in which this probably occurred.

CLINICAL AND PATHOLOGICAL REPORTS OF TWO CASES OF PYELO-NEPHRITIS.

Case XXIII. Ernest H., aged 7 months, the third child of healthy parents living in comfortable circumstances, was sent to the Children's Hospital by Dr. F. Porter on December 7, 1908. The complaints were drowsiness, fever, and abdominal pain, lasting for three days; and the child was taken into the Surgical Ward, under Mr. Stiles, as the case was thought at first to be one of acute peritonitis.

The baby was on the bottle, and had previously been fairly healthy, but he had suffered at times from indigestion, on account of which his milk was peptonized. There was no history, however, of diarrhoea or vomiting, nor of any other symptom of disease.

The onset of the illness had been sudden. On December 4 the baby was noticed to be drowsy, and towards evening he became very feverish, with quick breathing and frequent screaming as if in pain. There was no delirium, and

no fits or rigors. The abdomen was swollen and tender. The child was extremely restless and miserable, but appeared to have no pain on micturition. The use of hot fomentations to the abdomen seemed to give distinct relief.

The following day the drowsiness and the tenderness over the abdomen were much the same. There was no vomiting, but the child refused his bottle; the bowels moved twice, there were no fits or rigors. The temperature was 104°. On December 6 the temperature fell to 100°, but otherwise there was no improvement. On the 7th the temperature was again 104°, and the case was recommended for admission to hospital.

On admission the infant was found to be thin, with a clean tongue, pulse 130, and temperature 103°. The abdomen was somewhat distended, but it moved freely with respiration, and no tenderness could be made out, nor any enlargement of the liver or spleen. Examination of the blood showed a leucocytosis of 36,000, with 90 per cent. of polymorphs. A few rhonchi were heard over the lungs, but otherwise there was no sign of disease in the thorax, or in the abdomen apart from the urinary organs. The lower central incisor had just appeared.

During the next three days the fever continued (see Chart 9), and the child was restless and miserable but took nourishment well. On December 10 lumbar puncture was done and a little clear normal fluid removed.

On December 12 the diagnosis of acute pyelitis was suggested. This was confirmed on the 14th, when a large amount of pus, with *Bacillus coli*, was discovered in the urine, which was acid in reaction. Citrate of potash (grs. x) was given every two hours; and next day every four hours. By the 18th the urine had become alkaline, but the pus in the urine was not much diminished and the child seemed weaker. During the next two days the child continued to lose strength; and he died quietly on December 20 at 12.20 p.m.

Post-mortem examination, December 21, 1908. Body somewhat emaciated. *Thorax.* Thymus not enlarged. No pericarditis or endocarditis; myocardium pale and flabby; no pyaemic deposits. Small patches of lobular collapse in both lungs, no congestion, no pneumonic change, no pyaemic deposits. *Head.* No lesion of brain or membranes, except oedema. *Abdomen.* No peritonitis; mesenteric glands slightly enlarged, not tuberculous. Stomach, intestines, pancreas, and suprarenals showed no abnormality. Spleen slightly enlarged, soft, and acutely congested. Malpighian bodies not very prominent. Liver showed cloudy swelling, but little evidence of fatty change.

Urinary organs. Bladder small, empty, and contracted; openings of ureters patent. Mucosa showed a moderate catarrhal change, but no marked cystitis; no haemorrhages in the mucosa and no abrasions of the surface. Left ureter dilated, especially near its upper end, and its mucosa there intensely congested. Right ureter very slightly dilated. On squeezing its cut end, near the kidney, a drop of muco-pus escaped.

Left kidney (Plate 4) large and flabby. On stripping the capsule, the stellate veins were found enlarged in places, but the surface was for the most part unduly pale. The surface was studded with collections of pyaemic foci in clusters. The individual foci were very small, but some of the larger clusters measured fully $\frac{1}{4}$ inch in diameter. Most of the foci were surrounded by a hyperaemic zone. On section the cortex was swollen and pale. Most of the pyramids were intensely engorged, and showed radiating lines of suppuration, extending into the corresponding portion of the superficial cortex. The deep cortex was especially swollen and contained some necrotic foci. The apices of some of the papillae were intensely engorged. The pelvis was slightly dilated. Its mucosa was hyperaemic, and in it, near the tips of several of the papillae, there were small areas of haemorrhage and some superficial erosion.

The right kidney was enlarged like the other and presented a similar appearance in every respect, but the condition was not quite so advanced.

Although the appearances in the cortex of the kidneys were rather suggestive of a general systemic infection, the impression left was rather in favour of the

view that the infection had been primary in the neighbourhood of the apices of the papillae.

Histological report of urinary tract. Bladder. Acute, patchy superficial catarrh, slight congestion in submucous coat; very slight evidence of acute interstitial change in the submucous tissues.

Left ureter. Acute inflammatory condition in the wall near the kidney, not much catarrh, but a cellular infiltration in the deeper parts. This was specially seen round the vessels, which were engorged. The majority of the cells present were of the lymphocyte type; but there were numerous larger mononuclear cells like endothelial cells, and also some polymorphs. In the lumen there was a large mass of inflammatory exudate, apparently not formed locally. This consisted mostly of altered fibrin and broken-down polymorphs.

The pelvis of the left kidney showed the same appearances as those seen in the left ureter; but the cellular infiltration and the hyperaemia were even more marked, and the surface was denuded of its epithelium in places.

The right ureter showed an inflammatory change precisely similar in nature to that of the left, but less in degree.

In the right kidney there was an acute diffuse suppurative nephritis, with intense vascular engorgement, and haemorrhage round the areas of suppurative change. The epithelium of the secreting tubules showed advanced cloudy swelling, with early catarrh. Some of the collecting tubules were markedly dilated and showed a catarrhal change. In most of these, however, the lining cells were flattened out, and had come to resemble endothelial cells. The majority of the cells in these dilated tubules were not catarrhal cells, but polymorpho-nuclear leucocytes, some of which were very well preserved, others degenerating. The glomeruli were engorged, and in places showed a hyaline degeneration of their capillary walls. Sections of the papillae showed acute catarrh of the covering cells and of those lining the calyces in relation to them. In some places the epithelium was almost completely shed. The subjacent tissues were acutely inflamed and showed a cellular infiltration, mostly with cells of the lymphocyte type. In places, the appearances certainly suggested that there had been an invasion of the kidney tissue through the mucous surface. Abscesses were numerous both in the cortex and the medulla, but the condition was so advanced that it was almost impossible to say where they had actually started from. Distinct embolic plugs of bacteria in the vessels could not be demonstrated, but numerous Gram-negative bacilli resembling *Bacillus coli communis* could be seen scattered irregularly among the pus cells.

The histological examination of the other organs confirmed the naked-eye examination, except that some acute toxic parenchymatous change was found in the pancreas.

Note. The exact sequence of events in this case presents some difficulty. The fact that the pyaemic foci were limited to the kidneys would at first sight suggest direct invasion from the genito-urinary tract. On the other hand, it must be admitted that in certain pyaemic cases in which the invasion has obviously taken place from the blood, suppurative foci may be practically limited to the kidneys. These cases, however, are usually associated with the ordinary pyogenic cocci (e.g. staphylococci), and in such cases it is generally easy to demonstrate emboli of the infective organisms in the capillaries. The affection, too, is more focal in its character. In this case it must be remembered that we are dealing with a pure *Bacillus coli* infection and the diffuse nature of the suppurative change is more suggestive of an ascending pyelo-nephritis. Though absolute proof is wanting, therefore, it seems quite justifiable to regard the case as of this nature rather than due to a general pyaemic process.

Dr. James Ritchie isolated, from one of the small abscesses in the kidney, a pure culture of *Bacillus coli communis* which gave typical reactions in every respect. Neither microscopically nor by culture was he able to find evidence of any other organism in the kidneys.

Case XXV. James T., aged 3 months, the illegitimate child of a very poor woman, was brought to Dr. Melville Dunlop at the Children's Hospital, on March 25, 1909, with the complaint of great pallor and weakness. Dr. Dunlop was kind enough to hand over the case to me.

The parents were healthy, but the mother lived in a one-roomed house amid squalid surroundings. The baby had been on the breast (along with the bottle) until admission, and took his nourishment well. There was no history obtainable of diarrhoea, vomiting, constipation, or fits, or of pains with micturition or at other times; and no other signs of disease had been noticed before the present illness. He passed urine freely, and no offensive smell had been observed. He was said never to have had any acute symptoms, but during the last six weeks he had been getting gradually weaker and paler. The mother did not, however, seem to have taken much interest in the child. For the last few weeks he had, once or twice every day, taken 'fits' in which he became rigid and his eyes squinted inwards. These only lasted a few minutes, and there was no shivering.

On admission the baby was extremely feeble and pallid. There were a few enlarged cervical glands on both sides. The heart and lung sounds were normal. The abdomen was rather distended, but nowhere tender. The liver and spleen were not enlarged. The temperature was normal or subnormal during the first week in hospital. It then rose to 102° and gradually fell to subnormal again. The urine was acid, and contained a trace of albumin and numerous pus cells and clumps of *Bacillus coli*. The blood examination showed red cells 1,084,000, white cells 6,600, haemoglobin 25 per cent.; no nucleated red corpuscles were seen. The child got gradually weaker, and died on April 9 in the evening. During the last twenty-four hours, there were indications of pneumonia.

Post-mortem examination, April 11, 1909. Body poorly nourished. No septic wound or external abrasion.

Thorax. Thymus not enlarged. Extensive broncho-pneumonia with slight pleurisy in both lungs. Pericardium and endocardium normal, ante-mortem thrombus in both ventricles, myocardium pale but firm, and no haemorrhages. No pyaemic foci in lungs or in heart. *Abdomen.* Peritoneum, stomach, and intestines normal. Mesenteric glands slightly enlarged, pale, and firm. Spleen slightly enlarged, firm, dark red on section; Malpighian bodies evident, but not too prominent. Liver showed some fatty change, apparently central in distribution. No pyaemic foci in spleen or liver. Suprarenals normal.

Urinary organs. Bladder distended with slightly turbid urine, no cystitis, ureteral openings patent. Both ureters distinctly dilated, especially the right. The left kidney was slightly enlarged, the stellate veins engorged, but no pyaemic foci on the surface or on section. The kidney substance showed only some cloudy swelling. The pelvis seemed normal. The right kidney was much enlarged, being about three times the size of the left; it measured 7.5 by 3.5 cm. and weighed 43 grammes. The organ was soft and flabby, and, on removing the capsule, diffuse hyperaemia was found over nearly the whole of the posterior aspect and over the upper end in front. The hyperaemic area was pretty sharply defined from the rest of the kidney surface, which was unduly pale. Scattered over this hyperaemic area were numerous small raised deposits of a yellowish white colour. These varied in size from a pin-point to rather less than the flat surface of a split pea. The larger areas were irregular in outline, and some at least were due to the fusion of smaller foci. Some were surrounded by a hyperaemic zone. On section, one of the larger areas was wedge-shaped, with its

base at the surface. The appearance seemed to indicate multiple septic infarcts. On section of the kidney, the cortex was seen to be swollen and pale, especially in its deeper parts. The deposits near the surface were necrotic rather than suppurative in character and there were no true abscesses. The pyramids were congested, especially towards their bases. Radiating up from the apices of the pyramids were pale yellowish white opaque lines, but there were no distinct suppurative foci. The apices of some of the pyramids were granular and hyperaemic. Some were distinctly eroded. A similar hyperaemia was present in the calyces in the vicinity; and in the substance of the pyramids, near the calyces, there were small haemorrhagic infiltrations. The pelvis was distinctly dilated, and its mucous membrane injected, slightly granular, and showed minute haemorrhages at some points. Lying free in the pelvis was a small shred of granular-looking lymph. The condition appeared to be one of acute ascending pyelo-nephritis definitely spreading from the pelvis and associated with acute toxic parenchymatous change in the substance of the kidney.

Cultures from bladder and pelvis, and from the necrotic foci in the kidney substance, gave a pure growth of a typical *Bacillus coli communis*.

Histological report of urinary tract. Bladder. Only a very slight inflammatory change in the submucosa at one place; for the most part the mucosa was perfectly healthy. *Left ureter.* The mucous membrane for the most part looked quite normal (Fig. 5). Here and there were patches of desquamative catarrh. Lying free in the lumen were numerous cells, practically all epithelial in character. At a few points there appeared to be some cellular infiltration below the mucous surface, and the wall of the ureter looked unduly cellular. A few of the cells were polymorphonuclear leucocytes, the majority were lymphocytic in nature, or locally derived connective-tissue cells. Towards the outer part, that is, outside the muscular coat, there were distinct areas of cellular infiltration; and, in places, the cells had a perivascular distribution. These cells were of the same nature as those mentioned above. In this same neighbourhood there was dilatation of vessels, the connective tissue was loosely arranged, and there appeared to be some fibrinous deposit.

Left kidney. The calyces appeared slightly dilated. There was a certain amount of desquamation (probably post-mortem) of the epithelial lining. There was no trace of cellular infiltration of the tissues in the immediate vicinity of the calyces or apices of the pyramids. The collecting tubules appeared slightly dilated, and were lined by columnar or cubical cells. The cortical substance appeared for the most part normal (Fig. 6). There was a certain amount of cloudy swelling and vacuolation of the protoplasm of the cells lining the convoluted tubules. The glomeruli showed nothing abnormal. There were no inflammatory foci in either the cortex or medulla.

Right ureter. In some parts the mucous surface appeared normal; in others there was distinct desquamative change. In the lumen were many desquamated cells, and between them were numerous small Gram-negative bacilli corresponding morphologically to *Bacillus coli communis* (Fig. 3). There appeared to be some dilatation of small vessels in the submucosa and muscular coat. Round those vessels there was cellular infiltration, and similar collections of cells were seen outside the muscular coat.

Right kidney. In many places the calyces and apices of the pyramids were entirely denuded of their epithelial covering (Fig. 1); in others there appeared to be active catarrh. Lying free in the calyces were masses of micro-organisms, apparently *Bacillus coli*. The submucosa over the pyramids and in the calyces seemed to be unduly vascular, and there was intense cellular infiltration of the subjacent tissues. The large collecting tubules (Fig. 2) were greatly dilated and the epithelium lining them was altered in character, the normal columnar or cubical cells being represented by much flatter cells, in places almost resembling endothelial cells. Most of these dilated tubules were filled with cells. Some of these were polymorphonuclear leucocytes, a few

eosinophilic; but many were large mononuclear cells with rounded nuclei evidently local in origin. Many of the latter were actively phagocytic towards leucocytes and red blood corpuscles. Between these cells an occasional red blood corpuscle could be seen and numerous bacteria (*Bacillus coli*). The connective tissue between these tubules was oedematous and very cellular. In the cortex, corresponding to the necrotic areas seen with the naked eye, there was intense granular disintegration, in places amounting to actual necrosis. Around those necrotic areas there was not the amount of vascular engorgement which one observes round embolic infarctions of systemic origin. The glomeruli showed no special change. In some of the smaller collecting tubules, high in the superficial cortex, clumps of *Bacillus coli* were seen (Fig. 4). No infective emboli could be demonstrated in the vessels of the part.

Note. The histological appearances support the view that infection of the kidney substance had been produced by a spread of the infective agent from the neighbourhood of the calyces. It appears possible that there had been extension directly up the collecting tubules. On the other hand, it is also possible that direct invasion of the tissues had taken place from the eroded pelvis to begin with, and that this had been followed by a spread towards the cortex, by way of the lymphatics or blood-vessels. The fact that the condition, so far at least as the kidneys are concerned, was unilateral apparently excludes the possibility of a primary systemic affection of the kidney through the general circulation.

A culture taken from the heart-blood, indeed, gave pneumococci and *Bacillus coli*. The presence of the former may, however, be readily explained by the lung affection, while either may be regarded as due to an absolutely terminal invasion. It may be mentioned that cultures from the spleen remained sterile.

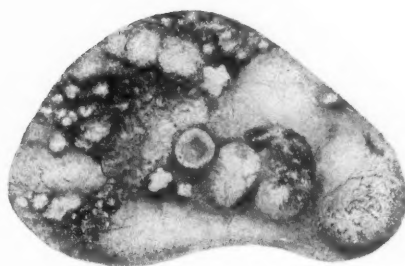
The histological examination of the lungs and other organs confirmed the naked-eye diagnosis.

DESCRIPTION OF PLATE 4.

Left kidney from Case XXIII, showing numerous pyaemic foci. Drawn by Mr. Richard Muir.

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Roxbur.

MICROSCOPIC SECTIONS FROM CASE XXIII
(Photomicrographs by Mr. Richard Muir)

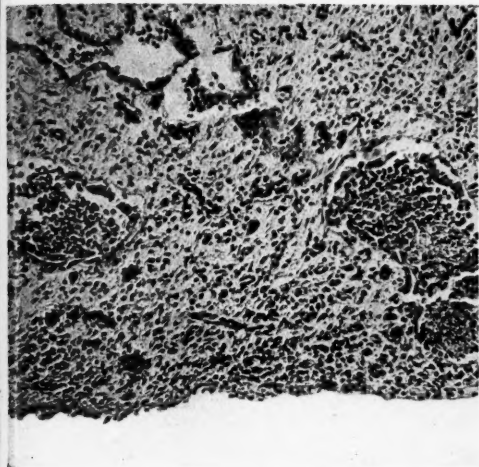


FIG. 1. Right Kidney. Surface of calyces. Excretory tubes greatly dilated and filled with inflammatory cells. $\times 140$ diam.

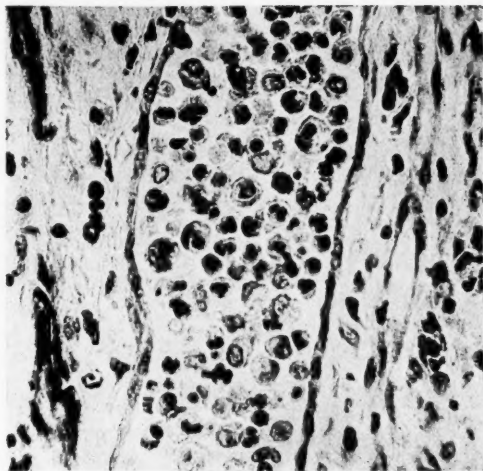


FIG. 2. Right Kidney. Collecting tubule filled with leucocytes and phagocytic cells. Flattening of tubular epithelium. $\times 500$ diam.

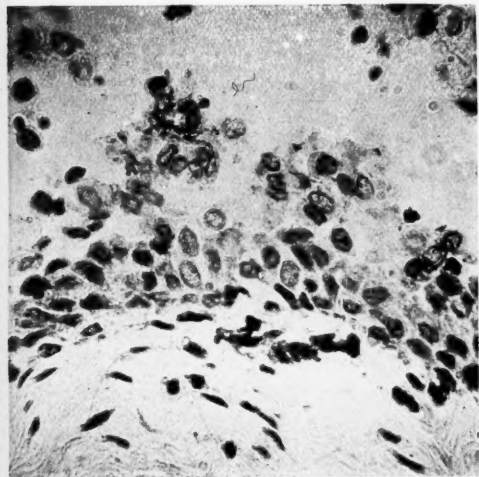


FIG. 3. Surface of Right Ureter. Catarrhal condition of epithelium and *B. coli* among the catarrhal cells. $\times 500$ diam.

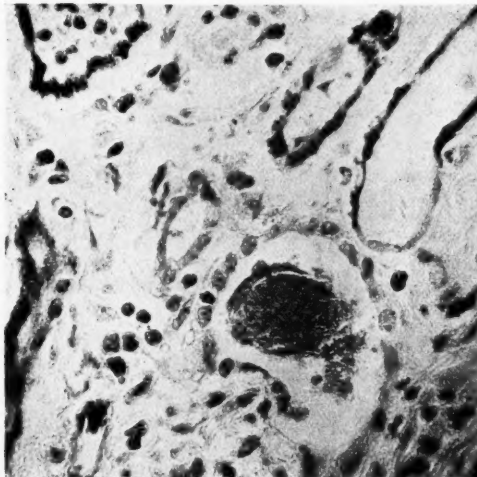


FIG. 4. Right Kidney. Mass of *B. coli* in the lumen of collecting tubules in the cortex. $\times 500$ diam.

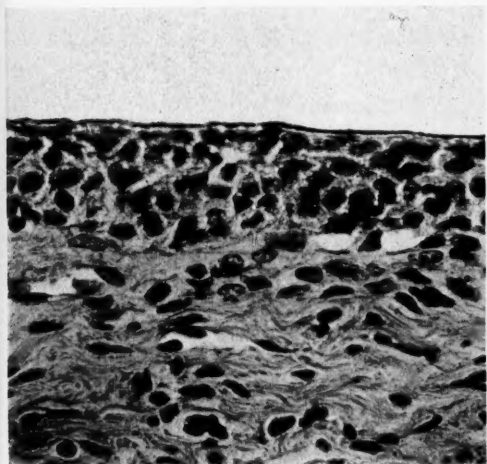


FIG. 5. Surface of Left Ureter showing normal appearance. $\times 500$ diam.

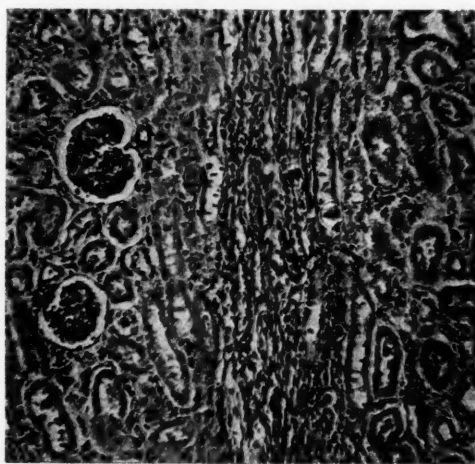


FIG. 6. Cortex of Left Kidney showing glomeruli and secreting and collecting tubules apparently healthy. $\times 140$ diam.



SO-CALLED 'BIGEMINY' OF THE HEART

By THOMAS LEWIS

(University College Hospital Medical School)

With Plate 6

IN his well-known work on irregularities of the heart, published in 1903, Wenckebach discussed bigeminy of the heart, and separated what he regarded as a special cardiac arrhythmia under the term 'true bigeminy'. He clearly recognized that the picture of paired beats arises in many instances as a result of extra-systoles, each falling subsequent to a ventricular systole having its origin in an auricular impulse. He regarded such examples of paired beats as lying outside a rational definition of bigeminy, and desired to restrict the term to instances of twin beats which present certain definite characteristics. The qualities of an isolated couple of beats, which he deemed it essential it should carry in order that it might be brought within the limits of the new definition, were two in number. First, that the second beat of the pair should lack a complete compensatory pause, and secondly, that the two beats should bear a constant time relationship to each other. In a later publication the definition was extended by the exclusion of the first qualifying factor. In brief, the definition was to include all instances of accurate coupling.¹ In dealing with the subject Wenckebach distinctly implies that the term bigeminy, to be logically employed, must be restricted to such of the twin beats as may be supposed to be constituted by individual beats of an identical nature. Such an implication involves the assumption that where beats are accurately coupled, the pairs consist of individual beats of an identical nature. It is in regard to this assumption that I wish to bring forward new evidence.

While examples of coupled beats may, at a given time, appear to consist of individual beats of an identical nature, yet as our method of examining such contractions is rendered more complete, it may be found that such couples are composed of beats which are essentially different. It will suffice if a single example is given in illustration of this point.² Since Wenckebach originally wrote on the subject, we have been provided by Einthoven with the means of readily ascertaining the electric changes accompanying the heart-beat. We are in possession of a new sense (through the medium of the string galvanometer),

¹ If I understand Wenckebach aright, the definition would not be required to include examples of coupling the outcome of ventricular silences.

² Another example was discussed in the *Lancet*, Feb. 6, 1909.

[Q. J. M., April, 1910.]

the natural outcome of which is the recognition of different qualities in objects which might formerly have been regarded as identical.

Amongst the examples of true bigeminy cited by Wenckebach, one of the most prominent was that of accurate coupling of contractions in complete auriculo-ventricular dissociation. An example of the condition has recently come under my observation, in a case from which Fig. 1 (Plate 6) was obtained. The figure demonstrates:—(1) three curves, of which the upstroke of each is marked by the letter *R*; they represent ventricular beats which belong to the ventricular rhythm proper; (2) three extra beats (each consisting of two main variations *Ep* and *En*) coupled at a constant time interval to a preceding beat of the ventricular rhythm; (3) and finally, superimposed upon the whole curve, a regular succession of auricular waves, marked *P*. The length of the pause following the extra beats varies slightly, but approximately corresponds to the pause between beats of the uninterrupted ventricular rhythm (the rate of this rhythm was 32 per minute on the same day). We are in the presence of an example of ventricular rhythm disturbed by a regular succession of abnormal ventricular contractions, all of a similar nature. It is believed that the beats of the ventricular rhythm proper have their origin at the point from which the ventricular wave of the normal heart-beat starts. The interrupting beats are those commonly designated ventricular extra-systoles, and they are of a variety such as can be shown, experimentally, to spring from an area of ventricular musculature lying to the left and in the neighbourhood of the heart's apex. The ventricular arrhythmia, as a whole, is therefore recognized as resulting from the alternate appearance of beats of two completely distinct types (i. e. beats springing from two separate foci in the ventricle).

A very similar example of an irregularity was reported in the succeeding paper of this Journal, but in this instance both the first and second beats of the couple arose from the point at which the normal ventricular beat starts. The fundamental rhythm may therefore be regarded as the same in each case, and the difference between them, as evidenced by the galvanometric curves, lies in the region from which the interrupting beats arise. The second example is reprinted in Fig. 2.

If the term 'true bigeminy' is taken to imply that the first and second beats of a couple are of an identical nature, the first example (Fig. 1) obviously lies outside the definition. In regard to the second example, it may certainly be argued that the impulses of the couple arise at the same focus, and that the contraction wave travels through the ventricular musculature in the same direction in each individual beat of the pair. But that the two beats are in every respect of an identical nature remains to be proved. The fact that one is invariably preceded by a longer and the other by a shorter pause is in itself sufficient to demonstrate that in their production there is an essential difference. The variation in the length of preceding pause is a fundamental distinction. The longer pause represents the time taken for the building up of a single intrinsic and physiological ventricular impulse. The shortened pause preceding the second beat

may be interpreted either as a result of phenomenally rapid impulse formation, or as a result of the inefficiency of the preceding systole in abolishing an impulse already generating. In either case an essential distinction remains. To speak of the condition as an example of bigeminy, meaning by bigeminy that the beats of a couple are of an identical nature, is therefore impossible.

When beats are linked together at accurate intervals for a considerable time, it is probable, as Wenckebach suggests, that the second beat of the pair is the direct result of the first. It might be convenient to apply the term bigeminy to arrhythmias in which this phenomenon may be supposed to exist. But here also we are met by a difficulty. Irregularities in which beats are coupled over long stretches of curve, but in which the coupling is not quite accurate, are well known. There is every possibility that in these instances also, the second beat of a couple is the offspring of the first, and there appears to be no sufficient reason for a sharp distinction between the mechanism of production in one case and the other, when it is regarded from this point of view.

It consequently seems advisable that the term bigeminy, employed in any sense other than that of the coupling of beats, should be allowed to lapse; at all events, until the time when we are in fuller possession of the facts in regard to the irregularities which we have been considering.¹

¹ Since this note was written, other examples of exact coupling, in which the separate beats of a pair have distinct points of origin, have been observed. An instance of coupling as a result of the interposition of auricular extra-systoles is given in *Heart*, 1910, i, Fig. 17. The well-known coupling in auricular fibrillation is due to the interference of ventricular extra-systoles (*Heart*, 1910, i, No. 4).

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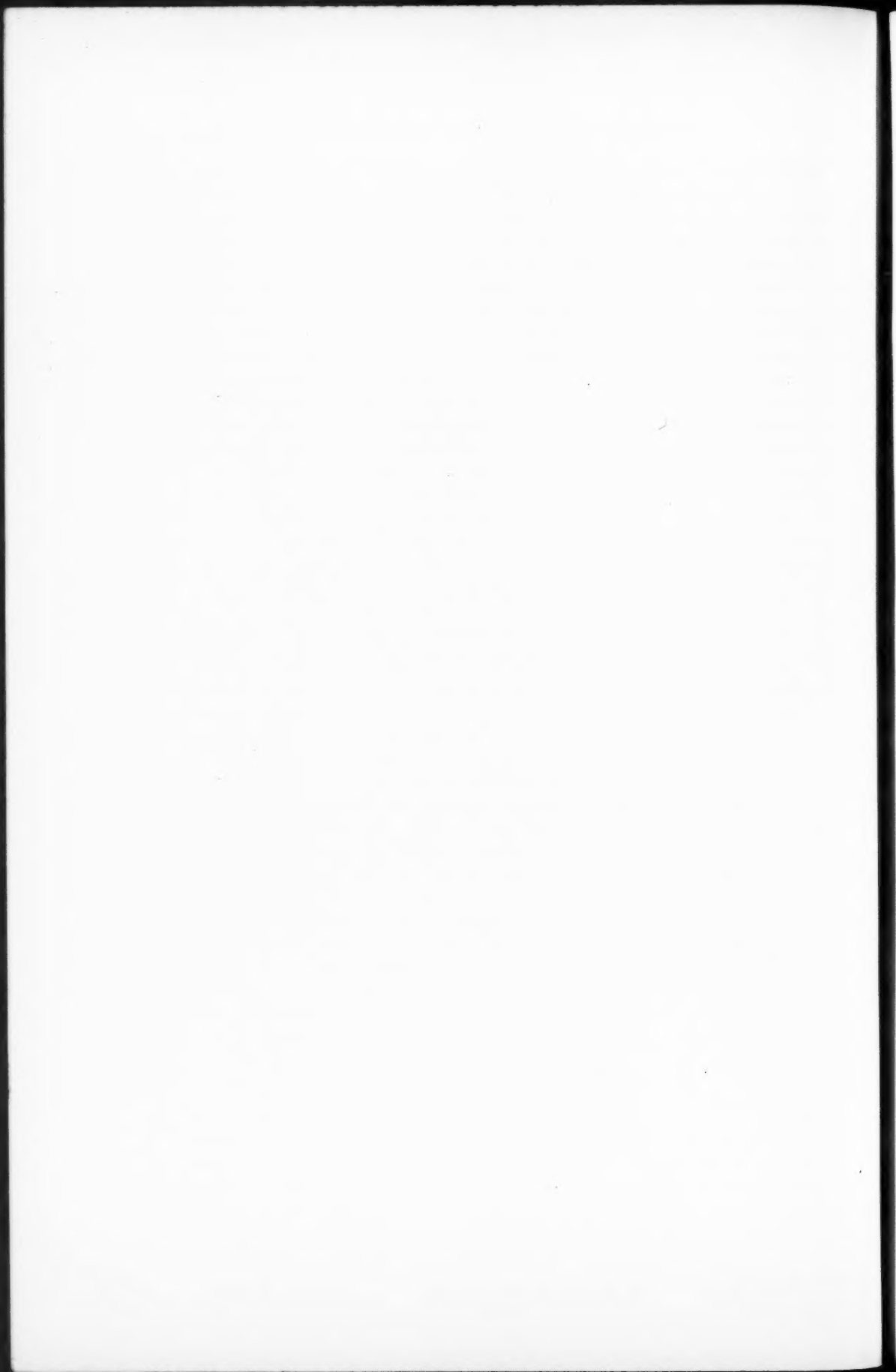




FIG. 1

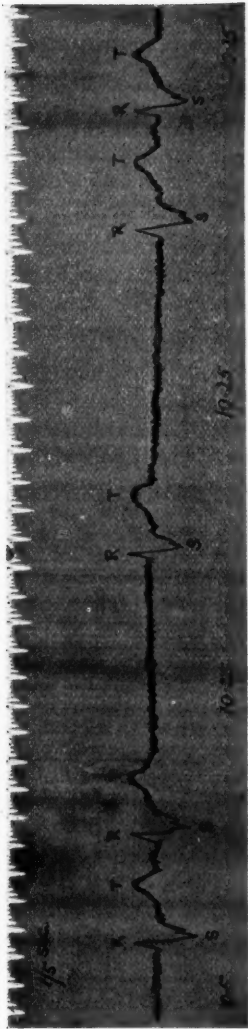


FIG. 2



COMPLETE HEART-BLOCK AND AURICULAR FIBRILLATION

By THOMAS LEWIS AND E. GARVIN MACK

(From University College and University College Hospital, London)

With Plates 7 and 8

At the present time it is believed that the normal contraction of the heart arises in those portions of its musculature which represent the morphological inlet. The exact situation of the representative (or representatives) of the amphibian and reptilian sinus tissue in the mammalian heart is still uncertain; nevertheless it can be located within certain limits. It is known that it lies somewhere in the auricle, and that it is closely connected with the termination of the veins in this chamber. In man, the origin of impulses at the normal starting-point is recognized by special records which indicate that the sequence of contraction in the chambers of the heart is normal. In a clinical instance of disordered action of the heart the ideal steps in the analysis of the case are:— (1) The determination, within the narrowest possible limits, of the focus from which those impulses are propagated, which constitute the dominating rhythm or foundation rhythm in the ventricle; (2) the similar localization of the points of origin of extraneous or ectopic impulses, which, if present, disturb the fundamental rhythm, whether the latter is normal or pathological; and (3) the determination of the events occurring in the auricle and their relationship to ventricular events. For all parts of the heart musculature are functionally rhythmic, and it is probable that all portions of it are capable of originating rhythmic and isolated contractions under special circumstances. In the present connexion special attention should be drawn to the rhythm of the ventricle when isolated, and to the remarkable constancy of its rate when it is cut off from the normal rhythm centres.

In the following pages an instance of the method employed in the investigation of disorderly action of the heart, along the lines indicated above, will be found. The case which we have chosen for this purpose is one which has been briefly recorded by Mackenzie; and we are indebted to Dr. Mackenzie, who has permitted us to undertake a fuller investigation of this patient.¹ The observations have extended over a period of eighteen months, and have been

¹ We have also to express our thanks to Dr. Bradford, Dr. Bolton, Dr. Russell, and others, under whose care the patient remained while certain of the observations were carried out.

made in several hospitals and infirmaries. For the space of six weeks the case was under the constant supervision of one of us, and during this time one of the fits occurred. It is described later.

History, &c.

M. M., male, born 1865. The patient was an old soldier who had seen service in India, and had since travelled in several countries. He had never suffered from rheumatic fever, scarlet fever, or joint pains. He was affected by dysentery in India at the age of 20, and two years later contracted *syphilis*. The venereal history was definite, for in addition to the chancre he also suffered from sore throat, a body rash, and 'breakings out' in the legs whenever he was in poor health. At the age of 27 he had malaria in America. He admitted excessive indulgence in alcohol up to the age of 40, and had always been a heavy smoker. The patient had never married, and there was no point of interest in the family history.

His illness began with a syncopal attack in 1894; he had a second attack a year later. He had been treated for 'mitral disease' ever since. He suffered on several occasions from oedema of the legs and shortness of breath, but recovered sufficiently to earn his living by clerical work until a severe breakdown supervened in 1905 and left him helpless. He had had many 'fits' from the year 1904 onwards. They had been attended with complete loss of consciousness and slight convulsive movements. In October, 1906, he had a severe fit, during which his pulse-rate was said to have fallen to 4 beats per minute. In June, 1908, he had a series of fits, but remained free from them until March, 1909, when the attack which is described occurred. In June, 1909, he had a further seizure. He stated that he was always forewarned of an approaching fit by dimness of vision. He considered that his latest seizures had been induced by gastric disturbance, more especially by flatulence. During the attacks he had never passed water or bitten his tongue.

Condition between the attacks. The patient, a tall thin man with a slight stoop, had a muddy and slightly flushed countenance. He walked slowly and deliberately, for upon the least exertion discomfort and dyspnoea supervened. His general nutrition was poor.

The pulse was slow and the rhythm regular; in rate it rarely varied outside certain limits (27 to 35 per minute) and was usually 30. The radial wave was gradual in onset, was prolonged and well sustained. The blood pressure was usually 140 mm. Hg.; a good deal of arterio-sclerosis was evident. The veins of the neck were full and the visible pulsation was prominent.

The maximum impulse of the heart was forcible and localized, and was found $7\frac{1}{2}$ inches from the middle line in the sixth interspace. A general diffuse shock was also felt over a larger area below and outside the nipple, and extending outwards as far as 9 inches from the middle line. The outermost point at which the thrust of the heart could be felt was at a distance of 9 inches from the middle line in the sixth interspace. No thrills could be felt. The limits of the cardiac dullness as defined by deep percussion were as follows: the upper border was found to lie beneath the third interspace, the left border at the mid-axillary line (9 inches from the mid-line), and to the right the dullness extended $2\frac{1}{2}$ inches from the mid-line. Over the region of the impulse a loud blowing systolic murmur was heard, partially replacing the first sound of the heart. The systolic murmur could be heard all over the axilla, and was traced to the epigastrium, where a slight diastolic shock was felt. At the apex the murmur was followed by a short sharp second sound, which in its turn was succeeded by a faint diastolic murmur. This murmur was not invariable, and when present was limited to a small area on each side of the anterior axillary

line in the sixth and seventh interspaces. It was short. The heart sounds over the rest of the praecordium were distant; there was no accentuation or alteration of the sounds at the base. A dull and distant sound was heard over the apical region and in the fourth and fifth interspaces to within 1 inch of the sternum, and followed the sharp second sound of the heart after a brief interval.¹

The physical signs in the lungs were those of emphysema, and several rhonchi were audible over the front of the chest. The liver dullness extended from the sixth rib downwards to the costal margin. The spleen was not palpable. The urine, examined on several occasions, never showed any abnormality. The patient was an intelligent man, but of uncertain temper. His pupils reacted equally and well. Examination of his nervous system in detail showed no abnormality.

Special Examination.

A. Polygraphic records. The radial and apical tracings, taken between the fits, as a rule show the beats to be absolutely regular (Fig. 1). The jugular curve presents a large wave occupying the period of systole. This wave commences at the instant at which the carotid pulsation appears in the neck and nearly 0.2 sec. after the apex beat. The form of the complete pulsation is inconstant; at times it presents a straight plateau interrupted by a dip in the centre of it; more frequently it consists of two definite waves of which the second is by far the larger (cp. figures). The commencement of the fall of the plateau (or the fall of the second wave) coincides exactly with the bottom of the downstroke of the apex beat. That the first wave is present in the veins is certain, for it is clearly visible in the external jugulars. *The radial pulse remains exactly regular within the error of measurement for long periods of time* (Fig. 1); but not infrequently it is interrupted by extra beats which present very definite characteristics. These beats are clearly felt and seen at the apex, and are accompanied by the first and second sounds and by the third distant muffled sound. In the cardiograms they are generally almost if not quite as prominent as the regular beats (Figs. 3 and 5). At the wrist the extra beats are usually small (Fig. 5), often absent (Fig. 3), not infrequently prominent (Fig. 2). Their prominence depends absolutely upon the time at which they occur in diastole. Measurements of the pause following such beats show them to be invariably shorter in the radial curve than the space between two ordinary beats, and this shortening varies with the height of the extra contraction as compared with the ordinary beat. Generally speaking, the difference in measurement between pause following extra beat and space between ordinary beats is absent in the cardiograms. The difference in measurement is due, in the main at all events, to an increase of the presphygmie interval accompanying the extra beat.²

¹ In June, 1909, the case was seen by Prof. W. S. Thayer of Baltimore, who remarked upon this sound, and declared it to be identical with the 'third' heart sound which Gibson and he have described.

² The increased delay may at times amount to 0.2 sec., and varies according to the position of the extra beat in the diastole of the preceding ordinary beat. (See Fig. 5.) The increased delay is present in the jugular curves, but to a less extent (Fig. 4).

The frequency of extra beats is very variable. They were recognized by the patient, who asserts that they were always more numerous in their occurrence when a fit was threatening. On the two occasions upon which his statement could be checked, it was verified. The extra beats are more frequent when the pulse-rate is slow. They are seen as occasional interruptions of the regular rhythm, occurring frequently after each second rhythmic beat (Figs. 2 and 6). They are found after each rhythmic beat less frequently (Fig. 3). In the radial curve they may produce slowing or the picture of a bigeminy. More rarely two extra beats may occur together (Fig. 5); when this occurs the pause following the last beat is equal to the space between two rhythmic adjacent beats. As in the case of the single extra beats, they are more or less prominent in the radial curve according to their proximity to the beats which precede them.

B. *Electro-cardiographic curves.* The curves taken with the string galvanometer¹ are exemplified by Figs. 6 and 7. The beats of the usual rhythm with leads from right arm and left leg (Fig. 6) consist of two main peaks, R and T, and one depression, S. The identification of the peak R with the peak similarly marked by Einthoven (a peak representing the onset of ventricular systole) has been arrived at by means of simultaneous curves, one a galvanometer curve, the other a radial or apex curve. The delays between electric and pulse or apex curves in these observations (examples of which are not reproduced) are compatible with the delays found in the normal subject, and with the presphygmie interval determined in this patient. Any sign of the normal auricular contraction during the diastole of the ventricle is absent from all galvanometer curves obtained; and the curve actually presented, consisting as it does of R, S, and T waves, may be compared to the *ventricular* curve obtained in the normal subject. It is deformed in that the peak R is dwarfed, while the depression S is exaggerated. This abnormality of the curve is of common occurrence when there is hypertrophy of the left ventricle, and, as would be expected from the percussion borders of the patient's heart, is well marked in the present instance. There is in addition a small bifurcation of the depression S which is unexplained. The curve shown includes five heart-beats, three of which belong to the usual rhythm, and two of which are extra beats. The first extra beat is followed by a pause of 10.25 sec. as in the next rhythmic beat. The galvanometer curves of the extra beats are identical in every respect with the rhythmic beats, even to the bifurcation of the depression S. The significance of these observations will be discussed in the sequel.

During the diastolic portions of the electro-cardiographic curve given in Fig. 6 some minor oscillations occur which are shown only obscurely in the figure. In later curves they have been much more distinct and their presence has been recognized as having a peculiar significance. Special observations were therefore undertaken to determine their exact origin. Fig. 7 gives the results of five dis-

¹ The expense involved in the production of these curves has been defrayed by a grant from the British Medical Association.

tinct leads from the chest-wall itself by means of special electrodes. The leads are arranged, as may be seen by reference to the explanatory remarks attached to the figure, so that in the first four curves there may be a gradual retreat from the right or superficial auricle. In the first curve an almost purely auricular curve is represented, in curve III the electric changes are those of the whole heart. In curves IV and V the changes are mainly those yielded by left and right ventricles respectively. The point to which attention is directed at the present time is that the irregular oscillations are maximal when both electrodes are placed over the right auricle, less when one electrode is so situated, and markedly less or even absent when neither of the electrodes is in this position. The different leads allow a partial separation of the curves yielded by auricle and ventricle, and enable us to conclude not only that the oscillations referred to are independent of somatic musculature, but that they are closely related to auricular activity. The method adopted, and the full significance of the curves, is discussed in the contemporary number of *Heart*.

C. *X-ray examination.* The patient was screened on three occasions, and the limits of the heart were defined. The left border was seen at the extreme left limit of the chest, while the right border was 4 inches from the middle line. The movements of the left border of the ventricle were clearly seen. The excursion was considerable both with rhythmic and extra beats. A very decided movement of the outline of the greatly enlarged right auricle was also seen, and was checked by several of those present at the examination. The movements in the centre of the outline seemed to be at least $\frac{3}{4}$ inch in extent, and gave the impression of a flattening of the outline. The movement is attributed to the pull of the ventricle.

The Attacks.

A fit occurred on March 18, 1909, at 11.30 p.m. For four days previous to the attack the patient complained of 'indigestion' and much flatulence. For several days previously frequent extra beats were noticed (Figs. 3, 4, and 5) though they had been absent before this. For a whole day preceding the fit the patient lay in bed fearing an attack. The abdomen was distended. The seizure commenced with a long-drawn inspiration, and soon the forehead was bathed in a cold sweat. The face, at first anxious, became expressionless and corpse-like in colour; the facial muscles twitched slightly. The eyeballs rolled round in all directions; they finally deviated upwards and to the left with the eyelids closed. The pulse at the wrist could not be felt, neither was there any impulse at the apex or other part of the præcordium. During this time the breathing was rapid and deep. The cheeks and lips were drawn in and blown out at each respiration with a noise resembling that produced by a patient under ether anaesthesia. There was no colour in the lips. The heart began to beat again, and with this the respiratory movements became slower and more shallow.

From the beginning of the attack the visible movements were as follows: the head was quietly moved from side to side, the left arm was flexed at the elbow and the hand placed at the side of the head, the right arm was extended by the side of the body. The patient was quite unconscious, and did not respond to painful stimuli. The pupils were found to react to light. At this stage a hypodermic injection of strychnine was administered. The seizure had now lasted about seven minutes, and during all this time *the external jugular veins had been pulsating vigorously* at about 140 to the minute, even though no pulsation was detected at wrist or apex. The neck pulsation continued at a rapid rate until beats increasing in rate were perceived at the apex and wrist. About two minutes later the series of events described above was repeated. The heart-beat could not be detected at the apex for forty-six seconds. During the next minute it contracted 43 times, during the succeeding minute 84 times, and during the third minute 120 times. All the beats came through to the radial pulse. Then for three minutes the rate of the heart dropped to about ninety, and a similar attack supervened. Soon after its cessation the patient opened his eyes and looked around him; he failed to recognize those at the bedside. The complete attack lasted twenty-six minutes, and terminated in his recognition of those around him. About ten minutes later he asked for some oil of peppermint. This was given; he refused to have his clothes changed, as he did not wish to be moved, even though they were saturated with sweat. He passed much flatus during the night. For the next two days the patient remained in dread of another attack, and on this account refused his food. No further attack occurred and he returned to his usual condition. No tracings were obtained during the fit.

At the beginning of June, 1909, the patient had another fit similar in every respect to that described. He was seen a week later, when he felt himself in imminent danger of a further attack. The pulse was thirty-six to the minute with frequent extra beats, as a rule 1 to 2 of the ordinary rhythmic beats. Whilst under observation the pulse gradually dropped to twelve per minute, and during a period of nearly an hour extra beats were only rarely present. Continuous curves were obtained during the whole of this time and most of the long pauses were due to complete standstill of the whole heart. It was noticeable that the patient's condition depended absolutely on the length of these pauses. When they were frequent he was restless and spoke only occasionally. With each of the longest pauses the restlessness was extreme, and the colour ashen. It is questionable whether the patient ever lost consciousness, even with the longest pauses, but with each of the latter his condition became obviously critical. The ears were deeply and the lips moderately suffused with cyanosis. The respirations were deep, slow, and embarrassed. Later, as the pulse quickened, the patient experienced great relief and recovered his colour. He complained of distension during the attack, and passed flatus continually. The hands and feet were very cold. The tracings consisted of curves similar to those which have been described already as occurring between the fits, with the exception

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that the pauses from one heart-beat to the next were greatly prolonged and not infrequently extended to time intervals of 20.5 and 22.5 sec. The venous tracings showed a single large or slightly bifurcated wave to each beat of the heart, and the dip following this wave was marked in its extent (Fig. 8). Measurements of the complete tracing are given in the accompanying table, in which the tendency for the long pauses to be of constant length is remarkable.

Table showing length of pulse-beats, during the observations made on June 5, 1909.

The measurement of each pulse-beat is in $\frac{1}{2}$ sec.

19.7	20.7	5.2	11.7	20.6	21.5
11.5	11.4	15.7	14.9	14.2	12.6
12.5	4.1	12.1	21.0	20.3	21.1
20.5	7.6	20.6	20.1	13.0	Interval of 7 m. 15 sec.
12.3	20.2	8.2	20.9	20.8	
20.3	19.1	12.2	20.8	21.0	
11.5	20.8	11.5	20.7	13.7	Interval of 7 m. 5 sec.
11.2	6.0	11.9	20.6	21.1	
20.6	6.8	21.2	12.9		
20.0	20.4	20.7	11.8	Interval of 7 m. 5 sec.	12.0
12.7	11.8	19.2	11.9		12.5
20.4	20.4	18.8	12.9		12.3
12.0	20.8	Interval of 6 m. 50 sec.	19.1	12.0	12.4
12.3	22.5		12.7	12.3	12.3
20.0	6.1		12.5	13.9	12.2
11.7	12.0		18.5	20.9	12.2
20.7	20.6	18.5	18.9	12.0	12.3
12.7	11.4	19.0	18.3	12.0	12.3
20.0	11.3	19.1	16.0	12.7	12.6
—	12.2	19.5	19.1	15.1	10.1
—	20.7	21.5	19.3	20.6	12.4
20.5	20.6	20.5	19.0	21.9	12.6
20.3	11.6	21.0	20.5	21.2	12.6
12.0	12.0	19.1	20.0	12.1	12.5
20.4	20.5	19.1	20.6	22.6	12.5
20.1	5.2	22.2	*20.7	21.1	12.8
—	15.5	21.3	20.8	11.5	12.7
—	12.0	22.1	20.9	11.1	12.4
—	13.3	21.4	20.8	11.6	12.6
20.1	20.8	20.9	*20.9	12.6	12.6
20.1	20.2	21.0	13.7	21.1	12.5
20.0	20.1	12.3	13.0	12.1	12.3
11.7	20.2	21.5	20.5	11.8	12.4
11.8	20.6	7.5	13.4	12.0	&c.
20.6	20.5	12.6	21.3	11.8	
20.1	11.9	11.8	21.2	12.0	

* Shown in Fig. 8.

The venous curves were necessarily irregular on account of the restlessness of the patient, and the more frequent oscillations towards the ends of the pauses (marked * in the figure) were the result of the increasing anxiety of the patient at those times. A short illustrative strip of tracing is shown in Fig. 8.

Discussion.

The facts at our disposal do not permit an exact diagnosis of the valvular condition of the patient's heart. There is no question but that the heart was

a very large one, and the enlargement included the left ventricle. It is improbable that such a degree of enlargement could be accounted for by mitral regurgitation. Neither were there any definite signs other than enlargement which would lead one to suspect the presence of adherent pericardium. The absence of a history of rheumatic fever, the absence of a constant diastolic murmur, the obscurity of the murmur when heard, the knowledge that such murmurs are not uncommonly reported in cases of so-called mitral stenosis, preclude us from forming a final opinion of the presence or absence of constriction of the mitral orifice. Taking the history of syphilis into consideration and the nature of the heart's rhythm, we are more inclined to the view that the main seat of the lesion was in the myocardium. Further discussion will be limited for the present to remarks on the nature of the cardiac mechanism.

The character of the galvanometer curves provides evidence of the commencement of *ventricular* contraction at a point in the ventricular musculature from which it normally starts; that is to say, we are led to the conclusion that the ventricle commences its contraction at the point at which it is connected to the auricle. Further, the nature of the curves, venous, radial, and electric, demonstrates that the beats of the ventricle start from a single point, whilst the heart beats regularly. The length of the pauses following the extra beats, and the complete absence of compensatory pause, show that the extra beats have their origin in the same focus as that from which the rhythmic beats arise. Further proof of this proposition is found in the galvanometer curves; for, as has been seen, the extra beats are in every respect duplicates of the others. We may therefore conclude, with a fair degree of probability, that all observed beats come from a single focus, and it remains to determine where that focus lies. The rate of the heart is thirty or thereabout, and a rhythm of this rate is the rule in cases of complete heart-block. In patients, the subjects of complete dissociation, the heart-beat is regular at this rate, and, as in this patient, the pause following an extra beat is equivalent to that between two beats of the ventricular rhythm. The similarity between the action of the ventricle in one and the other case is so striking as to carry conviction of their similar origin. The ventricular rhythm of complete heart-block probably arises as a result of impulses created in that portion of the *a-v* bundle which lies below the lesion which produces dissociation (the evidence for which will be found in Hering's paper and in the fact pointed out by Mackenzie that this portion of the bundle retains its normal microscopic appearance for many years subsequent to such a lesion). Consequently it is concluded that in this patient the rhythm arises in some portion of the node or *a-v* bundle. The regularity and rate of the rhythm at once suggest its physiological nature, for it is compatible with the findings of the ventricular rhythm in physiological experiment.

In ascribing the seat of ventricular impulse formation to the *a-v* node or bundle we have to assume a break in the functional continuity of musculature between those areas which normally give rise to the heart-beat, and those which are here active; that is to say, we must suppose a break between sinus and

ventricle. The parallel which this case offers to other cases of Adams-Stokes syndrome (the history of syphilis, the fits and their nature, and lastly, the regular slow beating of the ventricle) leads us, in view of certain considerations to be discussed presently, unhesitatingly to the view that we are dealing with a parallel pathology, namely, with a syphilitic lesion of the auriculo-ventricular bundle.

It remains to determine the events occurring in the auricle. We have seen that all signs of the normal auricular contraction are absent in the venous and cardiographic tracings. In the electro-cardiographic curves the normal auricular waves are replaced by oscillations of a very special nature, and it has been shown that these oscillations have their origin in the neighbourhood of auricular tissue. In what way are the oscillations produced and what is their relation to auricular activity? The answers to these questions depend upon the examination of a large number of patients and upon a comparison of clinical and experimental facts. The oscillations are due to fibrillation of the auricle, but the full evidence for this statement cannot be detailed in the present communication. It will be found in the contemporary number of *Heart*. Suffice it to say that when such waves occur upon the electro-cardiographic curves of other patients, they can be traced to the region where the superficial auricle lies, and that waves similar in every respect are produced by the auricles thrown into fibrillation experimentally. Now in the experimental instance and in other clinical instances it is customary to find complete irregularity of the pulse in association with this state. For the irregular impulses created in the auricle are transmitted in an irregular fashion to the ventricle. The unique feature of the present case is the additional presence of a lesion cutting off the ventricle from the auricular impulses which it would otherwise receive. Fibrillation of the auricle is of such common clinical occurrence that it is perhaps surprising that amongst the large collection of cases of complete dissociation co-ordinate contraction of the auricle has always been recorded hitherto. Admitting the frequency of the two conditions, an observation of a combination of the two was to be anticipated, and in the case under discussion we not only believe that the presence of both fully explains all the observed phenomena of the case, but that they cannot be explained in any other way.

The Nature of the Attacks.

The syncopal and epileptic manifestations which are so commonly associated with a slow action of the heart are as yet imperfectly understood. They are undoubtedly due to an extra slowing of the ventricle in the majority of cases; and in the slighter attack described in these pages the extra slowing of the heart from 30 to 12 beats per minute was sufficient to account for the symptoms observed. But to what the extra slowing is attributable is not manifest in the present state of our knowledge.

A different phenomenon observed in this case demands brief attention at this time. During the whole of the first attack described, a rapid movement in the

veins of the neck was recognized, and at times the ventricular rate rose as high as 120 beats per minute. In the absence of tracings it is impossible to decide whether the movement in the veins was auricular or ventricular in origin. A rapid and feeble movement of the ventricle alone cannot be excluded. Similarly a rapid and co-ordinate contraction of the auricle may not be placed out of court. Neither would the latter be inconsistent with the conclusion that between the fits the auricle is fibrillating, for a change from inco-ordinate to co-ordinate contraction in this chamber, or the reverse, is met with both clinically and experimentally. We have to deal with the fact that the ventricle beat during this attack at a rate approached on no other occasion during the whole period of observation. It is to this that we would draw special attention. A similar observation has been made in several cases of auriculo-ventricular heart-block, and reference may be made to the cases recorded by Wenckebach, Barr, Jellinek and Cooper, and Gossage. It might be suggested that in some such instances the rapid beats may be the result of an anabolic process following upon the cessation of vagal inhibition (as described by Gaskell). But it is improbable from the researches of Erlanger, Blackman, and Cullen (*Amer. Journ. of Physiol.*, 1908, xxi) that the vagus is involved in the production of fits where complete dissociation is present. Another explanation must therefore be found for the rapid beats, and the following is offered. One of us has shown that when the nutrition of the heart is seriously interfered with, as by ligation of a coronary artery, extra beats of ventricular origin may occur in rapid succession. When, in a clinical instance, the pauses from pulse-beat to pulse-beat are of sufficient length to interfere with the vascular supply of the brain (as manifested by the attacks of which we are speaking) a similar malnutrition of the heart-wall must also take place; and under these circumstances the awakening of a fast ectopic rhythm in the ventricle¹ might be expected.

Conclusions.

A case is described in which a slow action of the ventricle is associated with the ventricular form of venous pulse and with seizures of a syncopal or epileptic nature. Evidence is brought forward to show that the slow beats of the ventricle start from a point in the ventricular musculature at which it is joined by the tissues uniting it to the auricle, and that the impulses originating the rhythm start at a point not far removed from the auriculo-ventricular ring. The rhythm of the ventricle is interrupted by extra beats arising at an identical

¹ When the right coronary is tied and the vascular supply of both auricle and ventricle is affected, it is in the ventricle that the new rhythm arises. As has already been seen, we have certain evidence of rapid increase in ventricular rate in this patient. We have not definite evidence of a similar increase of auricular rate, but there seems no reason why, if such an auricular rate is developed, it may not be attributed to similar causes.

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focus, and this focus is near that from which the ventricular rhythm of complete heart-block springs.

It can be shown, on the other hand, that the auricle is fibrillating, but that the impulses so created are not transmitted to the ventricle, for its rhythm is regular. It is concluded that a lesion is present which completely breaks the functional continuity of auricle and ventricle. In brief, the heart mechanism is the result of (1) auricular fibrillation and (2) complete heart-block.

The fits recorded are of two kinds: the one is similar to those recognized as commonly accompanying *a-v* heart-block, and is ascribed to cessation of ventricular contraction; in the second variety, a great increase of ventricular rate was observed. Such increased frequency of ventricular contraction, during the prolongation of heart-block seizures, has been previously recorded on several occasions, and the suggestion is offered that in some such instances it may result from an irritation produced in the ventricle as a consequence of diminished blood-supply to this chamber of the heart.

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DESCRIPTION OF FIGURES.

FIG. 1. 9.iii.09. $\times \frac{5}{7.5}$ linear. Radial and venous curves. The radial curve is an example showing the usual regularity of the ventricular beats. The rate is 33. The venous curve consists of single waves divided into two peaks. The upstroke commences 0.1 sec. after the radial (line 3). The time marking is in $\frac{1}{5}$ sec. in all the figures.

FIG. 2. 25.iii.09. $\times \frac{4.5}{7.5}$ linear. Radial and venous curves. In this and subsequent figures certain lines are employed. 1 represents the upstroke of the cardiogram, 2 the upstroke of the carotid, 3 the upstroke of the radial, 6 the bottom of the downstroke of the cardiogram. The tracing shows the regular rhythm interrupted by extra beats occurring after each second rhythmic beat. The extra beats are prominent in the radial curve. The upstroke of the venous waves is synchronous with the carotid, the commencing downstroke with the opening of the tricuspid valves. The periods between lines 6 and 2 are $\frac{8.4}{5}$ sec. whether they are measured between rhythmic beats or an extra beat and the succeeding rhythmic beat.

FIG. 3. 13.iii.09. $\times \frac{3}{7}$ linear. Apex and radial curves. The tracing shows bigeminy of the ventricle. Extra beats following each rhythmic beat do not affect the radial tracing. The periods between lines 6 and 1 may be compared with those of Figs. 4 and 5, taken on the same day.

FIG. 4. 13.iii.09. $\times \frac{3}{4.5}$ linear. Jugular and radial curves. The tracing shows the normal rhythm interrupted by extra beats which just affect the radial curve. The interval between upstroke of jugular and upstroke of radial is less for the rhythmic beats (lines 2 and 3) than for the extra beats.

FIG. 5. 13.iii.09. $\times \frac{3.5}{5.5}$ linear. Apex and radial curves. The tracing shows the usual rhythm interrupted by numerous extra beats. The second rhythmic beat is followed by a pair of extra beats. The pauses following extra beats are approximately equal to the pauses between rhythmic beats. The transmission time from apex to radial varies very widely, being $\frac{0.9}{5}$ sec. for the rhythmic beat and rising to $\frac{1.6}{5}$ sec. for the extra beat.

FIG. 6. 9.vi.09. $\times \frac{6}{8}$ linear. A curve taken with the string galvanometer. It shows five ventricular beats, each consisting of R, S, and T variations. The extra beats yield curves which are exact duplicates of the rhythmic beats. The curve shows the compensatory pause following extra beats to be completely absent. The galvanometer curve has been retraced in black over the original.

FIG. 7. 17.xi.09. $\times \frac{4.5}{6}$ linear. Five separate leads from chest-wall, showing that the irregular waves upon the electro-cardiographic curves have their origin in the auricle. Each tracing shows $\frac{1}{5}$ sec. and electro-cardiogram. I. Arm electrode at the inner end of the third right interspace; leg electrode at the inner end of the fourth right interspace. II. Electrodes at the gladiomanubrial synchondrosis and at inner end of the fourth right interspace, respectively. III. Electrodes at the gladiomanubrial synchondrosis and at the apex, respectively. IV. Electrodes at the outer end of the third left interspace and at the fifth left interspace in the anterior axillary line, respectively. V. Electrodes at the apex beat and on the abdomen below and internal to the apex, respectively.

FIG. 8. 5.vi.09. $\times \frac{5}{14.5}$ linear. The tracing, consisting of jugular and radial curves, was taken during the attack which is tabulated in the text. The five beats shown are marked with asterisks in the table. The pauses are approximately equal and are each about 4 seconds in duration. The venous curve shows the regular wave occurring with each radial pulsation. The curve between the beats is irregular, and more especially towards the end of the pauses (marked *). As explained in the text, this irregularity is due to the movements of the patient as a result of his growing anxiety with the lengthening of each pause.

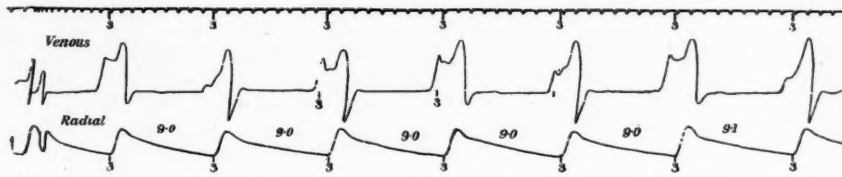


FIG. 1

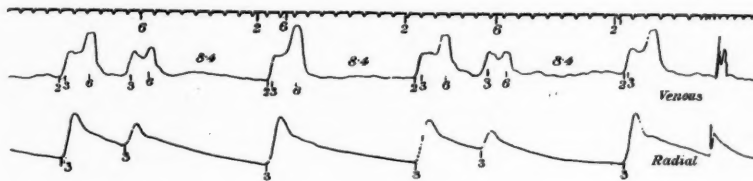


FIG. 2

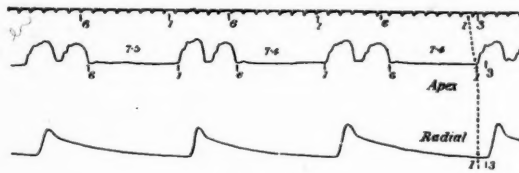


FIG. 3

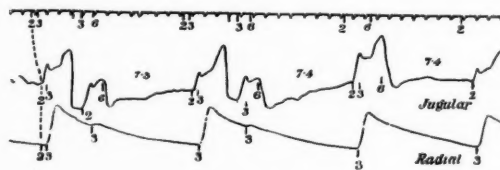


FIG. 4

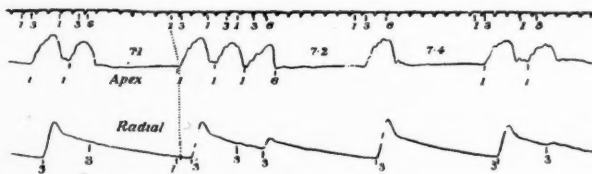


FIG. 5

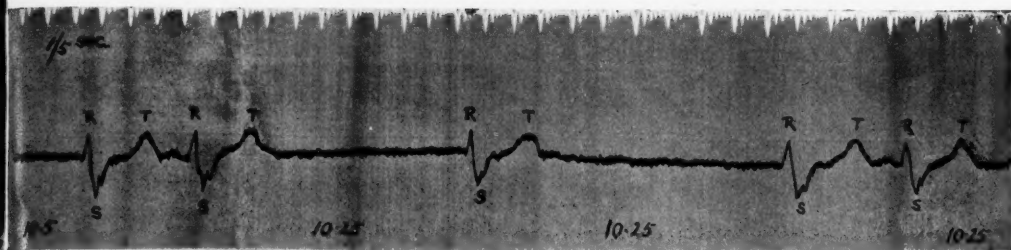


FIG. 6

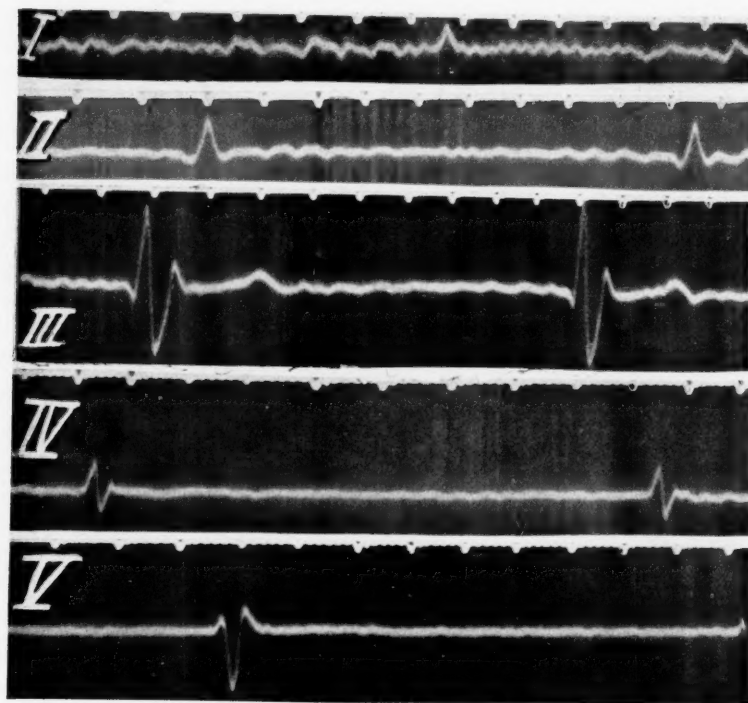


FIG. 7

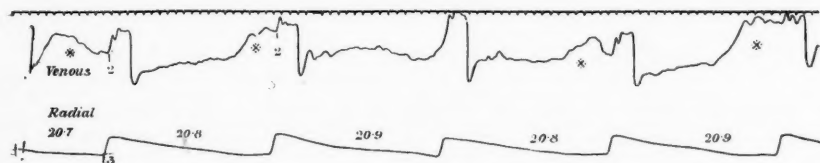


FIG. 8

ON THE PRESENCE OF HAEMAGGLUTININS, HAEMOPSONINS, AND HAEMOLYSINS IN THE BLOOD OBTAINED FROM INFECTIOUS AND NON-INFECTIOUS DISEASES IN MAN

By LEONARD S. DUDGEON AND H. A. F. WILSON

AN ABSTRACT OF THREE PAPERS COMMUNICATED TO THE ROYAL SOCIETY

(From the Pathological Laboratories, St. Thomas's Hospital)

THIS paper is for the purpose of introducing certain results which have been obtained by allowing normal and immune human serum to act in the presence of normal and immune blood cells,¹ and is an abstract of the work on this subject published in full in the *Proceedings of the Royal Society*, B, Vol. 80, p. 531, B, Vol. 81, p. 207, and B, Vol. 82, p. 67.

Nature of the Cases investigated.

The cases which have been investigated included almost all infectious and non-infectious diseases met with in this country, but attention has been mainly turned to acute pneumonia, pulmonary tuberculosis, acute peritonitis, acute infections due to the bacilli of the typhoid and paratyphoid family, all varieties of anaemia, more particularly with regard to pernicious anaemia and including cases of myelaemia and congenital family cholaemia; cases of acute streptococcic and staphylococcic infections; numerous cases of epilepsy and various miscellaneous examples, including purpura, jaundice, chronic renal disease, eclampsia, lead-poisoning, and coal-gas poisoning.

Haemagglutinins.

The technique adopted for observations on this subject may be briefly summarized from the papers already quoted as follows:—

The blood was withdrawn from the finger and collected in 0.85 per cent.

¹ The expressions 'immune cell' and 'immune serum' are used to designate the blood cells and sera taken from cases of any general disease or condition. The term 'immunity' is not confined, in this paper, to the series of phenomena resulting from bacterial infection alone.

sodium chloride and sodium citrate. The corpuscles were centrifugalized and freed thoroughly from the plasma by washing in sodium chloride. The blood was also collected in glass tubes and centrifugalized at the end of an hour, when clotting had taken place, as by this means a serum was obtained free from haemoglobin.

For the agglutination tests, one measured volume of a 5 per cent. suspension of washed red cells was drawn into a capillary tube with an equal volume of serum; these were thoroughly mixed and incubated for half to one hour at 37° C. in the horizontal position. At the expiration of this time they were blown on to a slide and examined microscopically. In many instances the agglutinative action was obvious to the naked eye.

Undiluted red cells. In some cases after the red cells had been washed in saline and the supernatant fluid pipetted off, a mixture of one volume of serum and one volume of undiluted red cells was made, but in those instances where negative results were obtained with the 5 per cent. red cell suspensions, similar results were also obtained with the undiluted red cells.

Haemagglutination.

Shattock, in 1899, communicated a paper to the Pathological Society of London on chromocyte clumping in acute pneumonia and certain other diseases. His observations were carried out for the purpose of determining whether the blood of patients suffering from acute pneumonia, erysipelas, or acute rheumatism, had any effect upon the rouleaux formation of normal human blood. He found, by adding one loop of normal human blood to one loop of pneumonic serum, that the chromocytes ran together. It is interesting to note that in all these observations mentioned by Shattock, which were the first on this subject in human haematology, he always employed *normal human blood* and added to it immune serum. In 1900 Grunbaum made a preliminary report in the *British Medical Journal* on the agglutination of red blood corpuscles. He came to the following conclusion as a result of his preliminary investigations: 'While the serum from a case of typhoid fever would clump the corpuscles in the blood from another disease, it did not clump the corpuscles from the same disease. The same held good for scarlet fever.' It appears from the investigations which we have made that it is extremely common to obtain agglutination by allowing normal serum and immune red cells, or normal red cells and immune serum, to interact.

Normal blood. At this point it is necessary to refer to a few facts in connexion with normal blood. The samples of blood used in these experiments have been obtained from workers in these laboratories and others apparently in the best of health. It has been found that some samples of normal sera have the power of agglutinating almost all specimens of normal red cells presented to them, and the agglutination may be of the haemolytic type, but in no

case has auto-agglutination or autohaemolysis been met with. The haemagglutinating properties of *pooled* serum were also tested. The results of these experiments may be briefly summarized. It was found that if a serum had caused agglutination of certain red cells, agglutination still occurred in the *pooled* mixture, but to a less degree according to the degree of dilution employed; but if no agglutination of the suspension of red blood corpuscles had taken place in any of the individual sera before *pooling*, no effect was noted when the pooled serum was added to these red cells.

In a certain proportion of samples of normal blood examined for agglutinative properties a negative result was obtained, but some specimens, while not exhibiting true agglutination of the individual chromocytes, showed a definite clumping of rouleaux; the appearance of this type of agglutination was extremely rapid and could be watched under the microscope immediately after the specimen had been prepared.

Pathological blood. In the course of our investigations, which extended over some 300 cases, iso-agglutination was found to be of common occurrence, while auto-agglutination was exceptional, only two true examples being met with.

It is important to note that the serum of one patient may agglutinate the red corpuscles of another patient suffering from the same disease; many instances have occurred during these investigations. In two cases of typhoid fever, e. g., the immune red cells of one case were agglutinated by the serum of the other and also by normal serum, consequently these results cannot be regarded in their present form as of the slightest value for clinical diagnosis.

Auto-agglutination. This phenomenon occurred in the case of a negro from the West Indies, who had not been out of England for over ten years. He was considered to be a case of tertiary hepatic syphilis, and he showed a blood possessing remarkable properties. When blood escaped from his thumb or ear from a single puncture, the red cells could be seen to be clumped in the plasma, and when the bleeding was continued into citrated saline the red cells fell to the bottom of the tube in enormous clumps. This is the only instance met with of a blood showing *spontaneous agglutination* and auto-agglutination of such a high degree. On the addition of the immune serum to normal red cells, marked agglutination occurred and it was of the true haemolytic type.

It has been shown that if an immune serum is diluted with normal saline it rapidly loses its power of agglutinating red cells quite out of proportion to what is observed in the case of the bacterial agglutinins. This sample of immune serum, however, clumped normal red cells when diluted to the extent of 1 in 10 almost as well as the undiluted serum, and some clumping occurred in a dilution of 1 in 500. This is the only instance out of the whole series of sera examined in which such a phenomenon was noted. When the negro's blood was tested about a month later, neither spontaneous nor auto-agglutination was present, but when the immune serum and normal red cells were mixed haemolytic agglutination occurred as before. One other case was met with in

a patient suffering from long-standing epilepsy; here, well-marked auto-agglutination was present, but not spontaneous agglutination, and the degree of agglutination was infinitesimal as compared to the blood of the negro.

The Relationship between Rouleaux Formation and Agglutination of the Red Blood Corpuscles.

In normal blood rouleaux formation is a constant factor. In certain acute and chronic diseases the rouleaux formation is either present to a slight degree or is absent. In those cases in which it is apparently absent it may be found that agglutination of the red cells is present instead. It will be seen, however, from previous statements that auto-agglutination is of rare occurrence, while iso-agglutination of one type or other is extremely common. It is, therefore, not strictly accurate to state that agglutination of the red blood corpuscles in certain diseases replaces or has replaced the rouleaux formation, because rouleaux formation, as we see it, is a true auto-effect—the red cells and the plasma from the same case. In agglutination it is generally otherwise, that is to say, the clumping of normal red cells in the presence of immune serum or vice versa is an iso-effect. Spontaneous agglutination in the blood obtained direct from the patient, such as may be seen in the experiments referred to, is of the greatest rarity, and only one case has been met with, that of the negro. Agglutination of rouleaux may take place in pathological blood; in some diseases it is very obvious, but here again the small clumps of rouleaux do not resemble actual agglutination of the red blood corpuscles. Shattock noted that if red blood corpuscles be mixed with serum diluted with saline the red cells did not form rouleaux. A similar effect is the rule in the case of agglutination. In this respect, rouleaux formation and haemagglutination have points in common. From an examination of the experimental data to hand, rouleaux formation and haemagglutination must be regarded as distinct phenomena although possessing certain points in common.

Haemolysis.

Technique. A 5 per cent. suspension of washed red cells in 0.85 per cent. sodium chloride in distilled water was employed for these experiments. Normal red cells were allowed to act in the presence of normal and immune serum, immune red cells in normal and immune serum, and normal and immune red cells in heated immune serum to which a definite volume of native or foreign complement had been added. The serum to be tested was always carefully noted to be free from any blood tinging.² The mixture of red blood corpuscles,

² So far in the whole of the blood investigations tinging of the serum or plasma with haemoglobin has never been noted, except owing to some error of technique.

serum, and salt solution was put into sealed glass tubes, placed in water at 37° C., and incubated at the same temperature for one to two hours. At the end of that time the tubes were put in the ice-safe overnight. The actual dilutions employed were from a mixture which contained 75 per cent. of serum down to one containing 12.5 per cent., or in some cases even lower dilutions.

In all these experiments on haemolysis, haemagglutination was present if haemolysis occurred; the haemolysing agglutinins could as a rule be detected from the pure agglutinins by the fact that many red cells at the margins of the clumps appeared as small retracted bodies, apparently less than half the size of the original cell and highly refractile. In the most striking instances numerous ghosts were present and the serum was strongly tinged with haemoglobin. In some cases the haemagglutination was much less than was to be expected, but this was owing to the powerful haemolysing action of the serum, which rapidly broke up the red cells.

Typhoid fever. Some very interesting facts arose in connexion with the haemolytic power of the serum in this disease. It was noted that when the *immune serum* caused *haemolysis* of *normal red cells*, the cases were of the *severe toxic type* and *terminated fatally*. It is true that the number of cases investigated is far too small to lay too much emphasis on this observation, but it is unquestionably important.

In the first case, immune serum caused marked haemolysis in the presence of normal red cells. In the second case, which also terminated fatally, an exactly similar result was noted; in the third case, the blood examined a few days before death and that obtained at the post-mortem examination gave a similar result, with the exception that the serum obtained during life had a slightly greater potency. In the remaining cases in which haemolysis occurred, it was due to the action of normal serum on the immune red cells. In every experiment immune serum and immune red cells failed to react; in fact, no other type of haemolysis occurred beyond that referred to.

The blood of a case of paroxysmal haemoglobinuria was examined during the acute stage and during the interval. The only exciting cause of these attacks was cold. The blood drawn from the finger in the usual way failed to show a red tinging of the serum when the usual precautions were adopted. It can be stated briefly that during the height of an acute attack the blood undergoes auto-haemolysis, but when tested as the attack subsides, although the man is obviously ill, no autohaemolysis can be demonstrated. The immune serum also failed to haemolyse normal red cells, and the immune urine and the immune red cells did not react. When, however, normal serum was added in definite measured volumes to the immune red cells, haemolysis occurred, although not to any very great extent, and haemolysing agglutinins could be similarly demonstrated. It would seem that the red cells themselves are principally affected, a point still further illustrated by the phagocytic experiments to be subsequently referred to.

The blood serum of two cases of diabetic coma obtained after death failed to haemolyse the immune red cells, but, as in the fatal cases of typhoid fever,

haemolysed normal red cells and agglutinated them strongly; in each instance haemolysis occurred down to a serum content in the mixture of 37·5 per cent.

The blood was examined very fully in twenty-one cases of pernicious anaemia, and of all diseases it might well be imagined that autohaemolysis could be demonstrated, but a negative result was obtained in every instance. It was found, however, that the immune serum had the same property of haemolysing guinea-pigs' red cells as normal human serum possessed. In three instances normal serum was capable of haemolysing the pernicious red cells to a marked degree; in each example haemolysing agglutinins were present, while in two out of the three cases marked phagocytosis of the immune red cells occurred in the presence of normal serum and normal leucocytes. In one instance, although normal serum haemolysed the immune red cells during the patient's life, yet the reaction failed to take place with the immune cells after death. It is interesting to note that in most cases the serum was of a canary yellow colour, due to the presence of a pigment which failed to give any spectrum, and which was not bile pigment; but in two instances bile pigment was definitely present.

Attention will be drawn later to the occurrence of haemophagocytosis in certain cases; this was usually most evident in those examples in which a serum had a marked haemolysing action on red cells.

The results of these experiments on haemagglutination and haemolysis are interesting owing to the fact that certain authors have advocated the transfusion of blood from one human being to another, when *in extremis*. It has been found from numerous observations that in many cases the serum of apparently healthy people possesses the property of agglutinating and haemolysing various types of immune red cells and even other samples of normal red cells, and consequently, should such a person whose blood possesses these properties be chosen for the purpose of transfusion, the results might be disastrous.

Splenic extract. Owing to observations made on the splenic cells in certain diseases in which much phagocytosis of the red cells occurs, it suggested itself that in the splenic juice might be found a substance or substances intimately concerned with phagocytosis, haemolysis, and certain other phenomena, although absent or present in an infinitesimal degree in the blood serum. The spleen from one of the cases of diabetic coma was extracted in a suitable machine, the thick lumpy extract filtered at high speed, and the centrifugalization repeated with the upper layer of extract which separated during the first stage. This final sticky, but *thin*, extract was used for testing the haemolytic effect on normal red cells and the auto-immune cells as in serum investigation.

In one instance the immune blood serum failed to haemolyse the immune red cells, and only reacted slightly in the presence of normal cells, the action being limited to a serum content of 37·5 per cent., yet the splenic extract was equally and strongly haemolytic to normal and auto-immune cells. The action was complete with a splenic content of 25 per cent. and limited to a mixture containing 0·25 per cent. of splenic extract. In a case of pernicious anaemia

which was investigated neither the immune serum nor the splenic extract haemolysed the immune red cells.

The Resistance of the Red Cells to Water containing Sodium Chloride of various strengths.

H. P. Hawkins and one of us (L. S. D.) showed that the red cells in two cases of congenital family cholaemia were especially susceptible to the action of hypotonic solutions of sodium chloride.³ The observations have since been confirmed by Hutchison and Panton. This investigation was undertaken with the idea that the red cells under various pathological conditions would show wide variability in their susceptibility to saline solutions, more especially in such a disease as pernicious anaemia and in the severe septic infections.

As already stated, the most interesting results were obtained in two cases of congenital family cholaemia; here haemolysis occurred in a solution of sodium chloride up to 0.6 per cent. In one case of virulent erysipelas a similar result was obtained, but otherwise the blood under various pathological conditions showed little variation from the normal; that is to say, haemolysis was prevented in a mixture containing 0.4 per cent. sodium chloride, and a reaction occurred in a 0.3 per cent. solution.

In all these experiments, with the exceptions referred to, the susceptibility of the red cells fell within the limits of the normal and no further information could be obtained, although the technique was modified in various ways, such as washing the red cells, adding sodium citrate and chloride in definite proportions, and working with a neutral fluid.

Haemophagocytosis and Haemopsonins.

Technique. The white cells were obtained by the method which is usually adopted for experiments on phagocytosis. A 5 per cent. suspension of red blood corpuscles in normal saline (0.85 per cent.) was used in every instance. One volume of normal or immune leucocytes was drawn up into a capillary tube with an equal volume of washed red cells and blood serum. These were carefully mixed, sealed, and incubated in the usual manner for fifteen minutes; film preparations were then made and stained with Leishman's stain. In some instances the serum was heated to 55°C. for thirty minutes, and the phagocytic properties of the serum were then compared with those obtained with the unheated.

Phagocytosis of the red cells was especially well marked in such acute diseases as typhoid fever, while in pernicious anaemia, contrary to our

³ Chauffard was the first to draw attention to the fragility of the red cells in this disease. The method employed in all these experiments was introduced by one of us.

expectation, it was usually absent. Care must always be exercised in arriving at conclusions on this subject, because, unless the film preparations are made with special precautions, red cells which are apparently engulfed are really extracellular, and also, if active haemolysis occurs in the phagocytic mixture, the red cells which are engulfed may be either too pale or too difficult to recognize, and therefore phagocytosis may be unknown.

The first marked instance of phagocytosis was in a case of jaundice of unknown origin. The immune red cells of the patient in the presence of the unheated undiluted serum from the same case and normal leucocytes gave a high degree of phagocytosis; 56 per cent. of the cells were phagocytic and there were thirty-three red blood corpuscles in the fifty cells. When normal red cells were used in conjunction with the same serum and normal leucocytes, as in the previous experiment, 76 per cent. of the leucocytes were phagocytic, and fifty of these contained forty-six red blood corpuscles. In a case of typhoid fever with typhoid pyuria a high degree of phagocytosis was noted. A mixture of normal leucocytes, immune red cells, and normal serum showed no less than thirty-seven red cells engulfed by fifty leucocytes. In this instance normal serum caused marked agglutination of immune red cells and also haemolysed them; in another case of typhoid, the phagocytic test carried out in an identical manner showed twenty-six red cells engulfed by fifty leucocytes, the normal serum in this case also acting as before. In a still further example the immune serum, normal red cells, and immune leucocytes gave an active result—fifty leucocytes contained thirty-nine red cells; when normal serum was added to the immune red cells, the phagocytosis was also well marked but to a less degree; in this case the immune serum strongly agglutinated normal red cells, but did not haemolyse them. Many more examples of this variety of phagocytosis have occurred in the numerous experiments which have been conducted, but the few cases recorded above are sufficient proof of this interesting and striking phenomenon.

It has been suggested that one of the main causes of anaemia is due to the presence in the patient's serum of a certain substance which acts upon the red blood corpuscles, which in turn became devoured by the leucocytes. There is nothing in these experiments to support this view. In the case in which the anaemia was most intense, the phagocytosis was present to an infinitesimal degree, while in the cases previously referred to, in which the phagocytosis of the red blood corpuscles was such a striking feature, the anaemia was of a mild type.

There was usually in these experiments no direct relation between the agglutinative, haemolytic, and opsonic content of a serum; in a few instances a serum possessed all these properties in about equal proportions, but generally, while the opsonic content was low or even absent, the degree of agglutination was strongly marked. As a general rule, whenever phagocytosis was well marked, agglutination of the red blood corpuscles was a still more striking feature.

Bacterial Phagocytosis.

In a paper published in the *Proceedings of the Royal Society* by Mr. Shattock and one of us (L. S. D.) it was shown that the immune leucocytes obtained from different sources may vary in their phagocytic value like the serum, and they considered that the only method of arriving at a correct estimation of the patient's haemophagocytic index was to allow the immune cells to work in the immune serum.

In the work which has recently been completed and which is here epitomized, these observations on the phagocytic property of the immune leucocytes have been entirely confirmed. No better illustration can be given than a case of pyaemia due to the staphylococcus albus: here the immune leucocytes, in the presence of normal serum and the organism isolated from the patient, showed a reduction of over 60 per cent. in their phagocytic activity as compared with that of normal leucocytes acting in the presence of the same serum and micro-organism. Two other experiments may be quoted in support of these facts. In the first instance, the immune serum from a case of pulmonary tuberculosis, acting in the presence of its own leucocytes and cocci, showed 174 cocci in 50 leucocytes, but when this immune serum acted in the presence of normal leucocytes and the same staphylococci, 50 cells contained 433 cocci. Again, in normal serum with normal leucocytes and the *Bacillus coli*, 50 cells contained 220 bacilli; but when the same serum acted in the presence of leucocytes from a case of acute lobar pneumonia and the same suspension of bacilli, 50 cells contained 83 bacilli.

We have shown still further, in a paper received by the Royal Society in September, 1909, that as immune leucocytes from different sources may vary in their phagocytic activity, so may leucocytes obtained from apparently healthy people, only to a less extent. In these observations on normal blood the number of leucocytes was approximately the same, so that the results of these experiments could not be in any way related to the number of leucocytes present per cub. mm. of blood. In every experiment on phagocytosis the serum which was examined within a few hours of removal from the body was free from blood tinging, and every experiment was made at about the same period.

It occurred to us that when the blood of one case was mixed with that of another or with normal blood the phagocytic results were not entirely dependent on leucocytes and serum, but might be partly due to haemolysis taking place in the phagocytic mixture.

Robert Muir, in a paper published in the *Proceedings of the Royal Society*, furnished evidence to show that when a serum was saturated with suitable red cells, its phagocytic value was very considerably reduced; this he considered to be due to the abstraction of the normal opsonin. In our experiments we have similarly found that when a serum is saturated with suitable red cells, its phagocytic value is considerably reduced, but that this does not occur in a mixture in which haemolysis is absent.

In Muir's experiments just referred to the mixture of serum and red cells was allowed to remain in contact for a prolonged period of time at 37°C. In our experiments, which were entirely confined to human blood, the mixture of serum and leucocytes, and therefore of red blood corpuscles, was only allowed to remain in contact for a period of fifteen minutes at 37°C., because this is the time which is commonly employed for the incubation of phagocytic mixtures when working with human blood. Therefore, if a reduced phagocytosis occurred owing to a haemolytic action, it must take place within a period of fifteen minutes, otherwise it would be of little practical importance.

We must very briefly refer to the method which was employed in these experiments, which are described in detail in the paper already referred to. The serum and leucocytes were collected in the usual manner in all these experiments. The serum was saturated with the washed red cells for fifteen minutes at 37°C., and at the end of that period the mixture was centrifugalized at high speed. By this means the phagocytic value of a serum could be ascertained both before and after saturation with suitable red blood corpuscles.

In every case the serum and red cells were also tested for their agglutinative and haemolytic properties. A few experiments may be quoted to show some of the results of these observations. A certain normal serum when mixed with normal leucocytes from another individual and an emulsion of staphylococci showed 270 cocci in 50 leucocytes; but after this serum had been saturated with these leucocytes and red cells for fifteen minutes at 37°C. and then centrifugalized, the serum, leucocytes, and staphylococci gave 94 cocci in the 50 cells. In this case it was shown that the serum had a powerful haemolytic action on the normal red cells employed, and we have as a result a greatly reduced phagocytosis. In a control experiment the leucocytes and serum from the same normal individual and the same organism gave a closely similar result before and subsequent to saturation.

It must be pointed out, however, that in some instances, though haemolysis occurs, there is no striking decrease in the phagocytosis, when the serum is saturated with suitable red cells. It also appears to be a fact that reduced phagocytosis is entirely related to haemolysis, and is unaffected by the presence of haemagglutination, to whatever extent this may occur.

A similar experiment to the above was carried out. In this instance, the immune serum from a case of acute pulmonary tuberculosis was found to have a powerful agglutinative and haemolytic action on normal red cells, when carefully tested. Therefore, as this serum haemolysed normal red cells, it was saturated with them, and the phagocytic value of a mixture of the immune serum, normal leucocytes, and *Staphylococcus aureus* before and after saturation was estimated, with the result that the haemolysis was shown to have caused a very greatly reduced phagocytosis.

It is unnecessary to cite any further experiments, as these merely serve to illustrate the relationship between phagocytosis and haemolysis as occurring in experiments with human blood. It would thus appear from these results that

the most accurate method of estimating the value of a phagocytic mixture is by employing a specimen of blood obtained direct from the individual together with the organism in question. By this means we obtain a true haemophagocytic estimate and avoid the errors that may arise owing to the use of leucocytes of unequal value, or of specimens of blood in which haemolysis is occurring during the incubation period of the phagocytic mixture; as already stated, these discrepancies may occur when any two samples of blood are mixed, whether they be immune or apparently normal.

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SOME REMARKS ON THE WORK OF ANDREW CONNAL

'A STUDY OF CEREBROSPINAL FLUID IN MENINGITIS'¹

By R. v. JAKSCH (Prag)

IN a series of investigations based upon the examination of the cerebrospinal fluid flowing spontaneously from the nose of a girl with a tumour of the brain, and numerous other cases, as meningitis and so on, I found²: The liquid is as clear as water, rather highly refractive, and in it there often float a few flakes, perhaps of fibrin or perhaps of mucin. Its reaction is alkaline, and the alkalinity is equivalent to 20–21 c.c. of a $\frac{1}{16}$ normal acid solution. The specific gravity is low, i. e. between 1.005 and 1.010. The fluid contains little albumin, and a large number of estimations carried out by me showed amounts varying between 0.03 and 0.05 per cent. The quantity of albumin, however, varies considerably, according as we are dealing with an acute or chronic morbid process. The chief proteid of the cerebrospinal fluid is serum-albumin, and I have failed to detect other proteids in quantities sufficient for their recognition.

The total nitrogen amounts to 0.01–0.05 per cent., sodium chloride to 0.79 per cent., phosphorus pentoxide to 0.01–0.02 per cent., and water to 98.87 per cent. I have always failed to find pyrocatechin. Urea is always present and in fairly constant amounts, 0.01–0.03 per cent. A carbohydrate can always be detected, which bears the closest resemblance in its chemical properties to glucose; however, it is not improbable that it is isomaltose. When estimated as glucose by titration with Fehling's solution, this carbohydrate amounted to 0.06–0.088 per cent., an average of twenty determinations. Standing in the air this carbohydrate disappears very quickly; even two hours after the taking out it cannot be proved.

Grünberger³ found at my clinic, in one case of diabetic coma, aceto-acetic-acid. It may be mentioned that the fluid sometimes contains acetates, but I have failed to detect carbamates and cholin in it.

As Hoke, working in my clinic, showed, the freezing-point varied, in observations made on different days, between -0.56°C. and -0.51°C. , and thus is very nearly identical with that of the blood (-0.56°C.).

Mercury, iodides, and salicylates given by the mouth, cutaneously, or subcutaneously, do not pass into the cerebrospinal fluid, as I showed conclusively in a series of exact experiments, and this fact is of fundamental importance as regards the whole subject of the absorption processes in the brain.

It would have been very interesting indeed to know how the last-mentioned phenomenon turned out in the great number of pathological cases investigated by Andrew Connal.

¹ This *Journal*, 1910, iii. 152.

² Cf. *Clinical Diagnosis* by R. v. Jaksch and Garrod, London, 1905, 482.

³ Grünberger, *Centralblatt für innere Medizin*, 1905, xxvi. 217.

[*Q. J. M.*, April, 1910.]

A VENTRICULAR VENOUS PULSE OF REGULAR RHYTHM

By E. E. LASLETT

THE patient, who was a labouring man aged 62, first came under my care in February, 1908. He had had a hard but very healthy life, and had been able to work up to Christmas of the previous year, although for a few months he had noticed that his breathing became distressed much more readily than before. At the beginning of the year his feet began to swell and he was obliged to give up work. When first seen there was considerable oedema of the genitals and lower limbs and some ascites. The legs were hard and brawny and the skin purple red. He was unable to lie down comfortably and was much troubled with a dry cough. The pulse was regular, of good volume, 82 per minute. The heart apex beat was fully 2 inches outside the nipple line, and the dullness extended well beyond the right border of the sternum. There was a loud systolic murmur at all areas, but louder outside the nipple, where it entirely replaced the first sound. There was an extremely well-marked venous pulse in

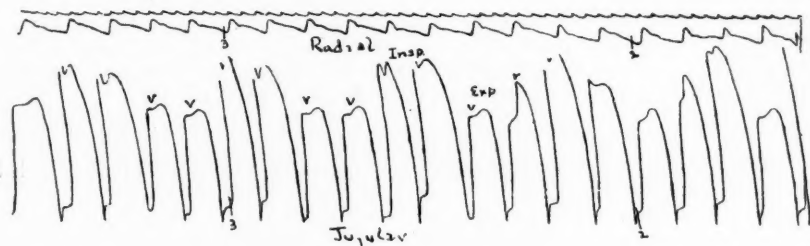


FIG. 1. Shows that the jugular pulse is of the ventricular form. Owing to a defect in the Dudgeon instrument the paper frequently moved more slowly after the first few inches had passed through. As the time-marker is not worked by separate clockwork, the frequency of the pulse in this figure, as also in Fig. 3 and parts of 4 and 5, is apparently greater than it was in reality. The respiratory undulations are well shown. May 28, 1908.

the neck, the sternomastoid being lifted up with each wave as far as the angle of the jaw. The size of the wave varied with respiration, being most extensive at the moment of inspiration. This was obvious on inspection and is also well shown in many of the tracings. If the breath were held in inspiration the wave remained at its increased size. Pressure over the region of the liver also markedly increased the size of the venous wave. I could not convince myself of the presence of liver pulsation, which may have been obscured by the presence of ascites, and I did not succeed in obtaining a tracing. Numerous curves taken at this time showed that the venous pulse was of the ventricular type. The radial pulse was always perfectly regular and showed remarkably little variation in rate, the most usual frequency being 80-84 per minute. Although digitalis (tincture) was given in 15-minim doses for weeks at a time it had absolutely no effect in slowing the heart.

For some months the patient declined to stay in bed, but at the end of May,

as the dropsy was increasing, he was persuaded to remain entirely in bed. On June 5 a Southey's tube was inserted into one leg, the head of the bed raised, and all added salt excluded from the diet. Although little more than a pint of viscid yellow fluid was withdrawn by the tube, improvement in the general condition began, diuresis set in, and in a few days there was a considerable reduction of the oedema. The venous pulse in the neck was now of much smaller volume, and a curve taken on June 10 showed that it had changed to the auricular type (Fig. 3). Improvement was maintained until the 20th; on this date it was found that the auricular wave had disappeared and the venous pulse was again of

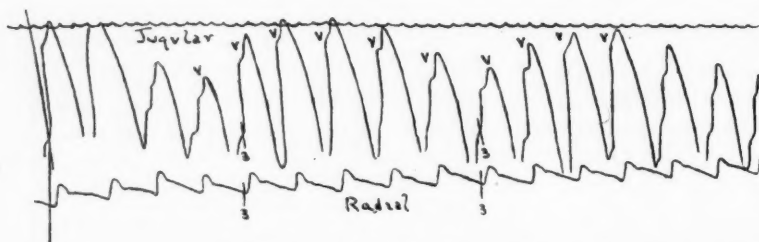


FIG. 2. Shows the same main features as Fig. 1. The respiratory undulations are slow here. The patient was attempting, but not very successfully, to hold his breath. June 3, 1908.

the ventricular type, and it remained so until his death. On the 24th *pulsus alternans* was noted for the first time. On July 2 the digitalis which the patient had been taking for some weeks was omitted. The pulse was now occasionally intermittent, and after each intermission the alternating character was greatly exaggerated and perceptible to the finger. The patient died on July 18, *pulsus alternans* having been present on the previous day.

From the history it seems probable that there was in this patient dilatation of the left side of the heart and mitral regurgitation, which had eventually led

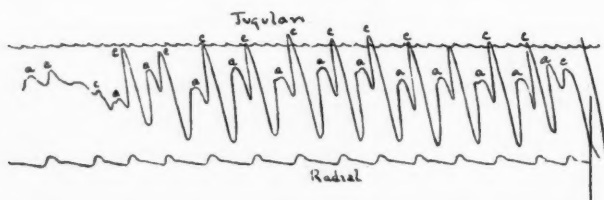


FIG. 3. Shows that the jugular pulse is now of the auricular type. For the greater part of the time the breath was held in inspiration. June 10, 1908.

to right-sided dilatation and marked tricuspid regurgitation. In his original description of the ventricular venous pulse Mackenzie divided the cases into three groups:—(1) Those cases in which there is auricular paralysis from over-distension secondary to disease of the mitral valves; (2) those cases in which there is no evidence of auricular action, but where the movements in the veins demonstrate that the rhythm of the heart is due to the ventricle; (3) those cases in which the auricle and ventricle can be demonstrated to contract simultaneously. From his later work Mackenzie has concluded that the majority of cases correspond

to Group 3, although he does not absolutely exclude auricular distension and paralysis as an origin of this condition. He finds that as a rule the ventricular systole commences one-tenth of a second before the auricular, and he has suggested that, owing to increased excitability as a result of some morbid process, the *a-v* node has now become the starting-point of the contraction stimulus, whence it is transmitted to auricle and ventricle. From these considerations the term nodal rhythm has been provisionally applied to this form of heart-action. In Fig. 1 the upstroke of the waves occurs one-tenth of a second before the radial pulse, therefore at the same time as the carotid and after the beginning of the ventricular systole. According to the nodal theory the first part of the wave must therefore be due to the auricle. Up to the time when the normal auricular contraction appeared the venous waves had shown little indication of a double peak such as appears in many of Mackenzie's curves. After the return to the ventricular rhythm this double peak was at first well marked, and the two waves were separated by a deep depression. Finally, the division into two

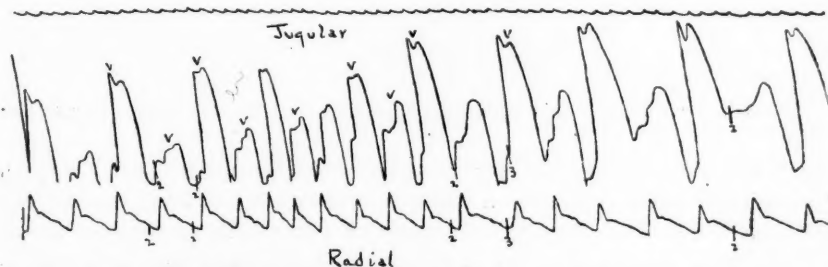


FIG. 4. Shows that the jugular pulse has again become of the ventricular type. The alternation in the radial curve is well shown. The tracing is marred by the irregular movements of the paper through the sphygmograph. July 16, 1908.

waves almost disappeared and the venous curve returned to its original form (Fig. 4).

In the majority of cases of nodal rhythm the heart is invariably and constantly irregular—hence the term *pulsus irregularis perpetuus* as applied to the radial pulse—the sole exception being in some cases of excessive rapidity of the heart. As a rule the pulse-rate in this condition is increased above a normal sinus rate, and in many cases the irregularity is extreme, large and small beats, long and short periods being inextricably intermingled. From physiological experiment it is known that the onset of auricular fibrillation is accompanied by complete ventricular irregularity. The possibility of the association of auricular fibrillation with *arrhythmia perpetua* has been indicated by Cushny and Edmunds, Wenckebach, and Hering. Recently Rothberger and Winterberg have developed this view. They find that the electro-cardiogram in nodal rhythm is, like that in experimental auricular fibrillation, specially characterized by a series of rapid small waves, most marked during the diastolic period, and they believe that in a number of cases the appearance of nodal rhythm is due to the onset of auricular fibrillation. In a preliminary communication

Lewis also gives the same explanation. He believes that the true nodal rhythm (in which the auricular rhythm is dependent on the ventricle) occurs only in one of the two types of paroxysmal tachycardia, and that the *pulsus irregularis perpetuus* is associated with auricular fibrillation, the disorderly nature of the ventricular rhythm being dependent on the irregular auricular movements.

The outstanding feature in the present case is the remarkable regularity of the rhythm associated with a moderate frequency, a regularity which under various conditions showed great constancy and was maintained for a period of at least six months. Von Tabora, in a paper on Tricuspid Regurgitation, gives a tracing of a regular pulse of 84, associated with a ventricular venous pulse, but he does not give the result of the case, nor mention the duration of the regular rhythm. Recently, in a paper on Nodal Bradycardia, Mackenzie gives tracings of a case in which with a pulse-rate of 40 the rhythm was perfectly

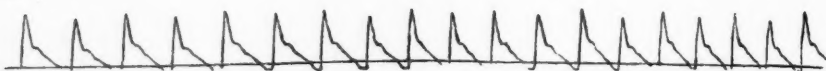


FIG. 5. Shows the alternating character of the radial pulse. There is an apparent quickening at the end of the tracing. June 29, 1908.

regular. In order to account for this abnormal type of slow nodal rhythm, he suggests that there may be a region between auricle and ventricle capable of inducing a rhythm of this kind, and that the disease in its progress has invaded and stimulated this area. Both experimental and clinical evidence point to the possibility of continuous stimulus formation at various levels of the heart.

The appearance of the *pulsus alternans* (Figs. 4 and 5) may possibly have been due to the action of digitalis, which the patient at the time had been taking for some weeks. As, however, it was still present a fortnight after digitalis was withdrawn, this is unlikely, and it is more probable that it was a terminal phenomenon of the dying heart-muscle. As already mentioned, at the last the pulse showed occasional intermissions, but unfortunately the only venous tracing I obtained which showed these was not completely satisfactory, but it appeared that the intermissions were due to premature ventricular contractions too weak to affect the radial artery.

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ON CHYLOUS AND PSEUDO-CHYLOUS ASCITES

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PART I.

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Introduction.

THE comparative rarity of chylous and pseudo-chylous effusions has led us to place on record the following observations. Continental writers in recent years, notably Bernert, Mattiolo, Polyakoff, Strauss, and Stryzowski, have published papers which have added considerably to our knowledge of the chemical and physical conditions that give rise to the peculiar character of these fluids. The milky-white opalescence of such effusions has claimed the chief attention of most observers, and attempts have been made to explain the causes that produce this appearance. We think that the facts now detailed will materially help towards the solution of the problem.

Abstract of Clinical Notes of Patient.

E. D., a male, aged 43, a joiner by occupation, was admitted to the Cardiff Infirmary on May 20, 1908, under the care of Dr. Herbert Vachell, suffering from chronic nephritis. The patient was well until October, 1907, when he caught a chill, and he then found his feet were swollen. He was laid up for a fortnight, and then started work again, but found that his legs and scrotum were swollen towards the end of a day's work. He was in this condition up to the time of his admission in May, 1908.

Condition on admission. The patient was a pale, anaemic-looking man, with good muscular development. The lower extremities were oedematous, the oedema extending up to the scrotum and loins.

Thorax.

Lungs: normal.

Heart: no evidence of hypertrophy.

Arterial tension high.

Second sound accentuated.

Abdomen: normal. No ascites.

Nervous system: normal.

Fundus oculi natural.

Genito-urinary system.

Urine diminished in quantity and loaded with albumin.

Microscopically many granular and hyaline casts.

The urine was examined for diamines and showed the presence of putrescin. The further details of the examination of the urine for diamines will be published separately at an early date.

A blood examination made on Nov. 3, 1908, gave the following figures:

Haemoglobin 70%.

Red cells $\frac{4,640,000}{13,500} = 1$ white cell to 343 red cells. Colour Index 0.7.

Differential Leucocyte Count.

Polymorphonuclear leucocytes	72.5 %
Lymphocytes	23.0 %
Large mononuclear	2.0 %
Eosinophiles	2.5 %
	<hr/> 100.0 <hr/>

The blood serum was found on examination to be perfectly clear. The Wassermann reaction for the diagnosis of syphilis was negative (November, 1909).

The patient remained in hospital for several months, until the ascites, which had developed since August 11, 1908, caused such discomfort that he was tapped on October 29, when 18 pints (10.5 litres) of a milky-white fluid were evacuated. The bulk of this fluid was inadvertently thrown away in the wards. One litre was available, and an analysis as complete as possible was carried out (*vide infra*). This is labelled Fluid No. 1. Paracentesis was performed a second time on February 24, 1909, and 20 pints (11.36 litres) removed. The whole of the effusion was secured, and the analysis is recorded under the heading Fluid No. 2. The oedema fluid removed from the legs on two occasions was quite clear.

The patient left the hospital on April 2, 1909.

General Characters of Fluid No. 1.

A white, milky fluid, odourless, and of a homogeneous character. On standing there was no evidence of any separation of a creamy layer, or of a deposit. The specific gravity was 1010, and the reaction to litmus is alkaline. There was no evidence of putrefaction even after several days: thereafter chloroform was added to the fluid and up to this date (November, 1909) no putrefaction had taken place. The fluid, however, after three months rapidly darkened, and finally became quite black. The microscopic examination of the fluid showed only a very few red blood corpuscles and leucocytes (lymphocytes), and a few fine granules. There was no evidence of fat globules, or of crystalline substances. The fluid was stained with osmic acid, and also Sudan III, and no change was produced in the fine granules that could be detected with the $\frac{1}{2}$ in. objective. 20 cubic centimetres were centrifugalized for an hour at 4,000 revo-

lutions per minute, and no deposit was obtained, the only change being the separation of a thin layer of a golden-yellow liquid fat. Filtration through filter-paper produced no change. The addition of ether did not clear the fluid.

Chemical Characters.

A. Qualitative.

(i) *Proteins.* Boiling produced no coagulation, even after the addition of acetic acid. Glacial acetic acid added drop by drop gave a white precipitate, which was soluble in excess of the acid. The following reagents also gave a precipitate when added to this fluid: nitric acid, potassium ferrocyanide and acetic acid, mercuric chloride, phosphotungstic acid, and picric acid. In all the above cases after the flocculent white precipitate had settled, the supernatant fluid was invariably quite clear. Alcohol gave a dense white precipitate which rapidly settled; the clear filtrate, which had a pale citron colour, on evaporation to dryness yielded a brownish residue, which was only partially soluble in distilled water. The alcohol precipitate was quite insoluble in water, thereby demonstrating the presence of coagulable proteins. The protein colour reactions, viz. the biuret, glyoxylic, Millon's, and sulphur tests, were all positive. Fibrinogen was tested for by the addition of fibrin ferment prepared from serum, but no coagulation occurred even after several days.

(ii) *Fats, lecithin, and cholesterin.* 50 cubic centimetres of the fluid were extracted with ether for a few days, and the extract treated with acetone and allowed to stand. A white, waxy, nodular deposit formed, which gave a well-marked phosphorus reaction. This was undoubtedly lecithin. The acetone solution was evaporated, and two distinct types of fat were noted in the residue, a white solid fat with a fairly high melting-point, and a yellowish liquid fat. The fatty residue was extracted with hot alcohol, and on cooling showed no separation of any crystalline body. Liebermann's and Salkowski's tests for cholesterin on the original fluid, and on the ether extract, were negative, thereby proving the absence of cholesterin in this fluid.

(iii) *Carbohydrates.* Tested with Fehling's solution a precipitate of cuprous oxide comes down after a distinct interval of time, and settles rapidly. Complete reduction of the Fehling's solution was never obtained. Moore's test, the safranin test, and sulphindigotate of soda test were negative. Treatment in the usual way for the preparation of osazone crystals produced a heavy yellowish-brown deposit, which on microscopical examination proved to consist of fine yellowish-brown needles arranged in spherical clusters, and in appearance resembling lactosazone. These crystals were embedded in an amorphous ground substance from which they could not be separated. An attempt was made to isolate the reducing substance revealed in the above tests. For this purpose the following procedure was adopted. The proteins were removed by treatment with hot alcohol, and the alcohol filtrate evaporated to dryness. A watery extract of this residue was slightly opalescent, and of

a brownish colour, and from this, on standing, a precipitate of a mucinoid character settled out. This precipitate was removed by filtration, leaving a filtrate which was still opalescent. Fehling's and Trommer's tests applied to this solution gave positive results. No protein colour reactions, however, could be obtained. To secure a polarimetric reading a portion of this opalescent solution was treated with alumina paste and lead acetate, well shaken and filtered. The filtrate was quite clear, and when tested with the polarimeter, showed no rotatory power, nor did it any longer reduce Fehling's solution or yield an osazone compound. It must be concluded that a sugar, as such, was not present in the original fluid.

A further attempt was made to deal with this question in the following way. The residual fluid, after extraction with ether, was taken and the above process again repeated. The polarimeter once more showed the absence of a rotatory substance. It was thought possible that the reducing body might be in combination with the lecithin present. The lecithin precipitate was therefore examined, but no reducing substance was present even after hydrolytic treatment.

The nitric acid and silver oxide reaction as devised by Baskoff gave also a negative result, showing the absence of jecorin.

Now since mucinoid substances such as paramucine give a reduction of Fehling's solution without any further treatment, but no osazone derivatives under the same conditions, the substance under consideration must clearly be of a more complex type. As reduction occurs in the original fluid and also in the alcohol filtrate, we may assume that this body is present in more than traces. Furthermore, alumina paste apparently carries down this substance, since no reduction and no osazone crystals could be obtained from the supernatant fluid.

Further remarks on this body will be made later in discussing the results.

(iv) *Organic extractives.* No traces of any free amino-acids could be detected. Creatin and creatinin were also absent. The fluid showed no traces of glycogen, bile constituents, urea, or uric acid.

(v) *Inorganic salts.* The presence of phosphates, chlorides, and sulphates, and the bases sodium, potassium, calcium, and iron were demonstrated.

(vi) *Ferments.* Varying quantities of the fluid were taken and Fermi tubes added, and left at room temperature for forty-eight hours. No digestive action was obtained. Our attention was called to the possible presence of oxydases by the gradual darkening of the fluid with the lapse of time (*vide supra*), in spite of the fact that chloroform had been added, and no bacterial contamination had taken place. A portion of the fluid was taken which was almost black, and showed a dark brown deposit, and to it was added an equal quantity of glycerine. The mixture was thoroughly shaken, allowed to stand for twenty-four hours, and then filtered. A few cubic centimetres of the glycerine extract were added to an alkaline solution of tyrosin in a test-tube, and incubated at 37° C. for twenty-four hours. The fluid at the end of this time

had darkened very slightly, nor did the addition of a ferrous salt produce any appreciable difference. A solution of tryptophane was similarly treated, and a very rapid darkening took place, which was further accelerated by the addition of ferrous sulphate. The presence of a tryptophanase and the possible absence of a tyrosinase were thus shown.

The following qualitative analysis was made of the blackened fluid for the purpose of discovering some of the changes that may have taken place. The reaction of the fluid was strongly alkaline, and of a specific gravity of 1015. It showed no absorption bands of the spectrum. The brown residual substance was removed by filtration and a portion was suspended in water. Boiling with a few drops of acetic acid rendered the solution quite clear. Testing this residue with Fehling's solution before and after hydrolysis gave no reduction.

Treating a portion of the residue by heating with fusion mixture and subsequent addition of nitric acid and ammonium molybdate gave a well-marked yellow precipitate, indicating the presence of organic phosphorus. This residue, therefore, contained the lecithin and also some protein. The filtrate from the above gave all the protein reactions, a well-marked reduction of Fehling's solution, but no other carbohydrate reactions. Addition of acetic acid gave a precipitate, which was soluble in excess, and also on boiling with a trace of acetic acid a precipitate was obtained. Basic lead acetate gave a dense precipitate, carrying down the pigment. Tannic acid (Cathcart's mixture) produced a similar dark-coloured precipitate. Half saturation of the fluid with $(\text{NH}_4)_2\text{SO}_4$ gave a brown precipitate, which was filtered off and suspended in water. It was partially soluble and gave a reduction with Fehling's solution, and also showed traces of phosphorus. This body behaved in every way similar to mucinoid substances. Complete saturation with $(\text{NH}_4)_2\text{SO}_4$ resulted in the production of a fine deposit which was only slightly pigmented and gave all the reactions for albumin. Filtration yielded an almost clear fluid which no longer reduced Fehling's solution though the test was carried out with all due precautions.

The remaining portion of the original filtrate on standing for a week deposited a typical mucinoid substance which gave all the characteristic reactions of such a body, i.e. precipitation by (a) acetic acid, (b) alkaloidal reagents, (c) potassium ferrocyanide, (d) lead acetate, (e) nitric acid, (f) half saturation with $(\text{NH}_4)_2\text{SO}_4$. Also it gave a reduction of Fehling's solution and yielded a glucosamine on hydrolysis. After removal of this mucinoid substance from the fluid, it no longer gave the reduction tests, but still contained albumin. It seems probable that the mucinoid substance had undergone decomposition, yielding a body closely resembling a melanin. No traces of a nucleo-protein could be detected in this fluid.

General Characters of Fluid No. 2.

A white milky fluid, odourless, and of a homogeneous character. On standing a thick creamy layer settled on the surface, and a scanty deposit collected at the bottom of the vessel.

The specific gravity was 1012, and the reaction was alkaline. Like the first fluid it showed no tendency to putrefaction. Chloroform was added as a preservative. Unlike the first specimen the fluid was as white when examined as it was when first drawn off. The only change noticeable was that the creamy layer had disappeared and apparently collected as a sediment. The microscopic examination of the fluid showed characters similar to that found in the first fluid. Centrifugalized the fluid showed a scum of yellow fatty material, along with a white creamy layer. The fluid portion, however, remained opalescent, and was indistinguishable from the mother liquor. Filtration through filter paper produced no change in the character of the liquid, but filtration through a Pasteur candle resulted in the production of a clear amber-coloured fluid. Addition of ether did not clear the fluid, and the further addition of caustic potash only served to increase the viscosity.

*Chemical Characters.**A. Qualitative.*

(i) *Proteins.* Boiling produced a slight coagulum, and the addition of acetic acid yielded a white flocculent precipitate. Treatment with the usual reagents enumerated above yielded definite precipitates. Adding an equal bulk of alcohol gave a dense white precipitate, which left a slightly opalescent filtrate. The residue was extracted with water and found to be quite insoluble, indicating the presence of coagulable proteins. The slightly opalescent filtrate gave all the protein colour reactions, reduced Fehling's solution, and gave the following precipitation tests: nitric acid, potassium ferrocyanide, and acetic acid giving white precipitates. Addition of a further quantity of alcohol resulted in a white precipitate, and the filtrate then no longer reduced Fehling. The mucinoid substance present in this fluid seemed to be partially soluble in dilute alcohol, but was precipitated when the concentration of the alcohol was increased. The fluid showed no trace of fibrin when treated with fibrin ferment. The protein colour reactions were all positive, especially the sulphur reaction, which was very strongly marked.

(ii) *Fats, lecithin, and cholesterin.* 500 cubic centimetres of the fluid were extracted with ether for some days, and the extract treated with acetone, a white waxy nodular deposit of lecithin separating out. The acetone solution was evaporated to dryness and two distinct types of fat were noted, a white solid nodular form melting at 44° C., and a yellow liquid form. No cholesterin could be detected.

(iii) *Carbohydrates*. Testing with Fehling's solution a precipitate of cuprous oxide came down after a distinct interval and settled rapidly just as in sample No. 1. The fluid, however, in striking contrast to the first sample, yielded no traces of osazone crystals. The same tests were applied as detailed above and no evidence was obtained of the presence of a sugar. The reducing substance was therefore not a carbohydrate.

(iv) *Other organic substances*. The same products as enumerated above for the first fluid were all absent. Diamines were present in traces.

(v) *Inorganic salts*. Chlorides, phosphates, sulphates, calcium, and traces of iron were detected.

(vi) *Ferments*. Adopting a similar procedure as in Fluid No. 1, it was found that no ferments were present.

B. Quantitative Examination.—Pseudo-chylous Fluid No. 1.

(i) For total solids, 100 cubic centimetres of the fluid were evaporated to dryness in a platinum dish. The residue was a brownish crinkled mass having a biscuit-like smell, and weighed 2.520 grammes. Incineration of this deposit gave an ash residue of 0.780 gramme.

(ii) The alkalinity, using methyl orange as indicator and $\frac{N}{10} \text{H}_2\text{SO}_4$, was 0.152 per cent. in terms of $\frac{N}{10} \text{Na.OH}$.

(iii) The total protein content was 0.652 gramme per cent.

(iv) *Fats and lecithin*. The two kinds of fat together weighed 0.8140 gramme per cent., and the lecithin 0.274 gramme per cent.

(v) *Inorganic salts*. The ash obtained was treated with 100 cubic centimetres of distilled water, and completely dissolved. The salts in solution were estimated by titration methods and gave the following results: Chlorides 0.603, phosphates 0.025 per cent. Sulphates present in traces only.

Pseudo-chylous Fluid No. 2.

(i) The total solids calculated on 100 cubic centimetres of the sample gave a figure of 2.741 grammes. The residue had exactly similar characters to that of the first sample. The ash residue was identical in quantity, viz. 0.780 gramme.

(ii) *Alkalinity*. This was approximately the same as the first sample. We say approximately because the end point of the reaction was not definite.

(iii) The total protein content was 1.220 grammes per cent. For coagulable proteins, 50 cubic centimetres of the fluid were taken, and an equal volume of alcohol added. A dense white precipitate settled down, which was repeatedly treated with hot alcohol, dried and weighed, and gave a figure of 1.161 grammes of total coagulable proteins. The filtrate, together with the alcohol washings, was evaporated down to dryness on a platinum dish, and yielded a residue closely resembling the original total solids residue in its colour and smell. This residue was incinerated and gave an ash figure of 0.492 per cent.

Precipitation by ammonium sulphate. One litre of the fluid was taken, and to it was added an equal bulk of a saturated solution of $(\text{NH}_4)_2\text{SO}_4$ well shaken, and allowed to stand for twenty-four hours. A white precipitate settled out on the surface of the fluid, which was separated by filtration.

The residue so obtained was treated as follows:—A suspension was made in water. It was found that but a relatively small quantity of the material passed into solution, for the greater part settled out on the surface of the water as a white creamy layer, which eventually settled to the bottom of the flask. The watery suspension was filtered with difficulty, and the filtrate remained slightly opalescent. Repeated washing of the precipitate with distilled water yielded a residue which was almost entirely free from the mucinoid substance. The residue was then extracted with ether, and the extract evaporated to dryness on a platinum dish, yielding a white solid fat melting at 45°C . The quantity was 0.1429 gramme per cent. There was no lecithin in the ethereal extract. From the residue a protein closely resembling serum globulin was separated, and also lecithin. Additional observations on this globulin are recorded later in this paper.

After removal of the precipitate obtained by half saturation with ammonium sulphate the filtrate was opalescent to a slight degree. Full saturation of the fluid with $(\text{NH}_4)_2\text{SO}_4$ resulted in a flocculent precipitate, which again separated out on the surface. The precipitate was filtered off with great difficulty, suspended in water, and gave a highly viscous solution which yielded all the protein tests, and in addition the reactions for mucinoid substances. The addition of glacial acetic acid produced a well-marked precipitate which was hydrolysed with concentrated hydrochloric acid, and yielded star-shaped crystals of glucosamin-hydrochloride on standing.

The filtrate after acetic acid had been added gave a coagulum and all the reactions for serum albumin. The serum globulin content of this fluid is 0.671 gramme per cent., and the serum albumin 0.490. The ratio of albumin to globulin is as 1:1.8. The total nitrogen as estimated by Kjeldahl's method gave 0.490 gramme per cent.

Fat and lecithin. 500 cubic centimetres of the fluid were extracted with ether for several days. Acetone was then added, and the lecithin precipitate collected and weighed, yielding 0.128 per cent. of lecithin. The phosphorus content of this lecithin precipitate was estimated by Neumann's method, as modified by Bayliss and Plimmer, giving 0.0096 gramme per cent. of P_2O_5 . The acetone solution was evaporated to dryness and the resulting fat weighed, giving 0.603 gramme per cent. of fat.

Inorganic salts. The quantitative analysis was carried out in three different ways.

(i) The ash obtained from 100 cubic centimetres of the original fluid was completely dissolved in distilled water made up to 100 cubic centimetres, and the constituents estimated; 0.780 gramme of ash gave 0.593 gramme of chlorides

calculated as sodium chloride, 0.028 gramme of P_2O_5 , 0.017 gramme CaO , and traces of sulphates.

(ii) The proteins were removed from 50 cubic centimetres of the original fluid by boiling with alcohol. The residue was repeatedly washed with hot alcohol, and the washings collected and evaporated to dryness.

The residue on incineration gave 0.492 gramme per cent. of ash, which yielded the following figures on analysis: Chlorides (as sodium chloride), 0.420 per cent.; phosphates (as P_2O_5), 0.028 per cent.; other constituents, i.e. traces of sulphates, &c., 0.044 per cent.

(iii) 200 cubic centimetres of the fluid were placed in a sausage dialyser immersed in 3 litres of pure distilled water. The residue after dialysis measured 230 cubic centimetres and the dialysate almost 2,970 cubic centimetres. The dialysate was alkaline and very slightly opalescent, but gave no protein reactions. An analysis of the dialysate gave 0.598 per cent. of chlorides estimated as sodium chloride, 0.0195 per cent. of P_2O_5 , and traces of sulphates.

Tabulating the results obtained by these three methods we have the following:—

Ash Constituents.		Alcohol Filtrate.	Dialysate.
Total ash	0.780 %	0.492 %	
Chlorides	0.593 %	0.420 %	0.589 %
Phosphates	0.028 %	0.028 %	0.0195 %
Calcium	0.017 %		
Other constituents, } Mg, Fe, &c.	0.142 %	0.044 %	

It will be observed from a perusal of this table that the percentage of chlorides, as sodium chloride, varies according to the methods of analysis. 0.589 gramme per cent. is quite dialysable, leaving 0.004 gramme per cent. as combined with the protein, and not removable by dialysis. This accords with the observations on adsorption compounds described by Bayliss.

Alcohol precipitation, however, produces quite a different result, since 0.173 gramme per cent. is represented as being combined with the protein, or rather carried down with it. The next noteworthy feature is the difference in phosphate content. Only 0.0195 gramme of P_2O_5 is completely dialysable, leaving 0.0085 gramme as in combination. This figure agrees very well with that of the organic phosphorus figure, i.e. the phosphorus present in the lecithin, viz. 0.0096 gramme per cent. The most striking feature, however, is the phosphate content of the alcohol filtrate, which corresponds exactly with the figure for the total P_2O_5 in the ash. This clearly proves that treatment with hot alcohol has completely removed the lecithin from the globulin.

Physico-chemical Characters of the Pseudo-chylous Fluids.

(i) The action of small concentrations of electrolytes.

Solutions used.

	$\frac{N}{1} \text{NaNO}_3$	$\frac{N}{1} \text{Na}_2\text{SO}_4$	$\frac{2N}{1} \text{Mg}(\text{NO}_3)_2$	$\frac{2N}{1} \text{MgSO}_4 \cdot 7 \text{H}_2\text{O}$
Pseudo-chylous Fluid No. 1	4 drops, no ppte.	do.	no ppte.	no ppte.
1 c.c. + 5 c.c. water	10 drops, no ppte.	"	ppte.	ppte.
	30 drops, no ppte.	"	ppte. compl.	do. complete
Pseudo-chylous Fluid No. 2	5 drops, no ppte.	do.	ppte.	ppte.
1 c.c. + 5 c.c. water	10 drops, no ppte.	"		
	30 drops, no ppte.	"		
Ascitic fluid	5 drops, no ppte.	do.	no ppte.	do.
1 c.c. + 5 c.c. water	10 drops, no ppte.	"	opalescence	
	30 drops, no ppte.	"	ppte.	
			$\frac{N}{2} \text{Ba}(\text{NO}_3)_2$	
Pseudo-chylous Fluid No. 1			do.	
Pseudo-chylous Fluid No. 2			5 drops ppte.	
Ascitic fluid			do.	

Since the fluids are all alkaline in reaction and are only precipitated by dibasic ions, we must assume that the particles in the fluid under consideration have a negative charge. At the same time it is of interest to compare the two fluids as regards the concentration of electrolytes necessary to produce complete precipitation.

An attempt was made to determine the rate of flow of the charged particles in this colloidal solution by means of the 'boundary method', but, owing to its low viscosity, a definite boundary layer could not be obtained.

The pseudo-chylous fluid No. 2 was exposed to radium rays of a strength of 400,000, according to Madame Curie's scale, in order to remove the electrical charge upon the colloid particles. Exposure to the radium emanations for a period of forty-eight hours resulted in a dense white precipitate settling at the bottom of the tube, and the supernatant fluid was only very slightly opalescent, and in appearance resembled ordinary ascitic fluid. Vigorous shaking of the tube restored the opalescence, but it only remained in this condition for a few hours. A white deposit soon separated, but the supernatant fluid was not so clear as previously.

The freezing-point determinations were made on both samples, and gave a depression of -0.59° for Fluid No. 1 and -0.61° for Fluid No. 2. (Ascitic fluid figure was 0.56° .)

Discussion of Results.

Both samples of the pseudo-chylous fluid examined present the same general physical properties. They represent typical colloidal solutions, and the particles in suspension give rise to the peculiar character of this fluid. The opalescence disappears as a result of exposure to radium rays, or by dialysis, or by filtration through a Pasteur candle. Centrifugalization or mere

filtration has no such effects. With regard to the protein content of these fluids little need be said of the serum albumin, which behaves in every way like ordinary serum albumin. It is, however, present only in very small quantity. The globulin, however, calls for some description, since it does not exist free in the solution, or only so to a very slight extent. It is for the greater part combined with the lecithin present, the combination being of the nature of adsorption. The lecithin can be removed from the complex by means of repeated treatment with hot alcohol, or by long standing under ether. Simple shaking with ether for a short time does not extract any lecithin. The stability of this complex seems to be increased when it is 'salted out' from solution, since it then requires hydrolysis by dilute acids to split off the globulin. The lecithin globulin compound, when isolated, is insoluble in most organic solvents, and shows very few of the properties of globulin itself. That this substance remains in solution is due to the inorganic salts present, for dialysis at once precipitates it, and the fresh addition of either dilute salt solutions or the solution of the ash constituents has no effect on the solubility. The remaining protein consists mainly of a mucinoid substance. This is exactly comparable to that obtained by Hammarsten from ascitic fluids, and is the agent which reduces Fehling's solution. The difference in the mucinoid of sample No. 1 seems very difficult to interpret, and the subject requires further investigation.

The fat as shown in the table is present only in small quantities, and this is confirmed by the microscopic appearances. The properties of the fats coincide with the observations recorded by others. The presence of lecithin is one of the most interesting features of this fluid. The character of its combination with the globulin present is of the nature of an adsorption compound. Attention might here be drawn to the remarkable resisting power of the fluid to putrefaction, which we think is probably due to the presence of lecithin. Filtration through a Berkefeld filter yielded a clear amber-coloured fluid free from lecithin but containing traces of proteins. This fluid putrefied at once on exposure in the laboratory, and the same occurred in the dialysed residue after the lecithin complex had been removed by filtration. This observation also finds support in the remarkable powers possessed by bile, and certain collections of pus which contain lecithin, of resisting putrefaction for a considerable length of time. This is one of the outstanding features of most of the pseudo-chylous and chylous fluids previously recorded. The absence of cholesterin, and also sugar, from these fluids is very significant. Furthermore, we do not find any traces of urea in either fluids.

The two most important inorganic constituents are the chlorides and phosphates. Dealing with the chlorides, it is found that 0.165 per cent. of the total 0.593 per cent. is in combination with the proteins.

Compared with the small quantity of protein present this figure is far in excess of that normally present as ash residue of protein. The phosphates (i.e. P_2O_5) in combination amount to 0.008 per cent., which may well correspond

to the phosphorus content of the lecithin present, and affords additional proof of the entire absence of nucleo-proteins in these fluids. The importance of the inorganic salts lies in the significant part they play in the production of the opalescence of the fluid. Removal of the salts by dialysis results in the precipitation of the lecithin-globulin complex, and the disappearance of the milky character of the fluid. Shaking up the lecithin-globulin complex with normal salt solution re-establishes the milky appearance, but it is not permanent. Addition of distilled water to this body has no such effect, it being quite insoluble in water. It may be concluded, therefore, that the milky character of the fluid is due to the presence of this adsorption compound, which is held in suspension by the salts present.

The absence of any cellular elements may provide an explanation of the presence of an excess of inorganic salts, and the relative abundance of lecithin in all effusions of a pseudo-chylous nature. The difficulty in accepting this explanation is the absence of any body resembling a nucleo-protein, though it would fully explain the quantitative ratios of the other constituents, and the differences between pseudo-chylous fluids and ordinary ascitic fluids. The addition of lecithin and serum globulin to ascitic fluid gives rise to an opalescence resembling in every particular a pseudo-chylous exudate, and similarly the lecithin-globulin isolated above, when added to ascitic fluid, produces a like pseudo-chylous fluid.

In the second part of this paper we propose to compare the results detailed above with those of other authors, and also to review the copious literature that has accumulated on this subject. At the same time we hope to give the results of another case, which Dr. Horder has kindly handed over to us for investigation.

Conclusions.

(i) The milky appearance of a pseudo-chylous ascitic fluid is due to a lecithin-globulin complex, which is held in suspension by the inorganic salts present.

(ii) Removal of the inorganic salts present by dialysis results in the precipitation of the lecithin-globulin complex, and the disappearance of the opalescence.

(iii) The milky appearance of the fluid is not due to free lecithin, fat, or a mucinoid substance.

(iv) The power of resisting putrefaction is due to the presence of lecithin.

Our thanks are due to Dr. Herbert Vachell for his kindness in allowing us to publish the facts of this case; to Professor Haycraft and Mr. Gowland Hopkins, F.R.S., for their interest and valuable criticism; and to Mr. W. B. Hardy, F.R.S., for his generous help in the determination of the physico-chemical character of the fluid.

REFERENCE.

Baskoff, *Zeitschr. f. physiol. Chemie*, 1908, lvii. 395.

CRITICAL REVIEW

THE MYOPATHIES OR MUSCULAR DYSTROPHIES

By FREDERICK E. BATTEN

With Plate 9

Introduction.

THE object of this article is to consider the present standpoint of our knowledge with regard to the group of cases known under the title 'Myopathy or Muscular Dystrophy'.

1. The first section of the article will deal with the classification of the myopathies, and especially with the relation of the condition described by Oppenheim under the title 'Myatonia congenita' with the myopathies.

2. The second section will deal with the question of prognosis and the curability of myopathy.

3. The third section will deal with the pathology of the various types of myopathy as illustrated by recent work.

It is not the intention of the writer to deal with the earlier history of the disease, but simply to put before the reader a review of the subject in the light of recent clinical and pathological observation.

The following classification of the muscular dystrophies is suggested:—

- (1) The simple atrophic type (Myatonia congenita or Amyotonia congenita).
- (2) The pseudo-hypertrophic type.
- (3) The juvenile type (Erb).
- (4) The facio-scapulo-humeral type (Landouzy and Déjerine).
- (5) The distal type (Gowers).
- (6) The Myotonia atrophica type.
- (7) Mixed and transitional types.

It may be assumed that the characteristic features of the pseudo-hypertrophic type, the juvenile type, and the facio-scapulo-humeral type are well known. The other suggested classes have not obtained such general recognition, and the characteristic features of these will therefore be described.¹

¹ It may be well to emphasize here the distinction between the similar sounding names, MYATONIA CONGENITA and MYOTONIA CONGENITA.

MYATONIA CONGENITA is the disease described by Oppenheim and characterized by loss of tone in the muscles. Collier and Wilson describe the same condition under the title *Amyotonia congenita*. It is a disease of infancy and early life. MYOTONIA CONGENITA is the disease described by Thomsen and characterized by the symptom that on the execution of a voluntary movement the muscles brought into play remain contracted for some seconds. It is a disease of early adult and adult life.

The *simple atrophic type* may be said to have the following features: The disease is congenital or starts in early infancy, and is characterized by smallness, lack of power, and loss of tone in all the muscles of the body, without localized atrophy or hypertrophy of individual muscles or groups of muscles. All movements are capable of being performed, but in a feeble manner. The disease is but slowly progressive, for the child may, as development takes place, learn to sit up, and possibly to stand with support. The child usually learns to talk at the normal age, and intellectually is often in advance of his years. As a rule these children never learn to walk, but adopt some strange method of getting about; the child will roll round and round in the long axis of the body in order to get from one part of the room to the other, or will assume a squatting attitude, and it is to this peculiar attitude that the name 'frog-child' was originally applied by Dr. Head to one of my cases. The position is illustrated in Plate 9. The feet and hands appear to be unusually long, and, owing to the extreme flaccidity of the muscles, can be bent at most unusual angles to the arms and legs. In the later stages of the disease, some contraction of the flexors usually takes place, so that the legs cannot be fully extended. Closely related to this condition is that described by Oppenheim under the title 'Myatonia congenita', and it is to the discussion of the relationship of this condition to the myopathies that the first portion of this article will be devoted.

(1) *Myatonia congenita and its relationship to the Myopathies.*

Myatonia congenita is the name given by Oppenheim to a disease characterized by a condition of extreme flaccidity of muscles associated with the entire loss of the deep reflexes, usually most marked at time of birth, and always showing a tendency to slow and progressive amelioration. There is great weakness, but no absolute paralysis of any muscle. The limbs are most affected, the face is almost always exempt. The muscles are small and soft, but there is no local muscular wasting. Contractures are prone to occur in the course of time. The faradic excitability of the muscles is lowered and strong faradic stimuli are borne without complaint. No other symptoms indicative of lesions of the nervous system occur. Since Oppenheim first called attention to this condition several cases have been published, and in this country the able paper of Collier and Wilson has done much to make the condition well known. Now it is claimed that this condition is clinically quite distinct from and has not yet been proved to be associated with the myopathies, and the following facts are brought forward in support of this contention:—

- (1) The myopathies are conspicuously familial diseases, whereas no familial tendency has been recorded in myatonia.
- (2) The several types of myopathy often show familial relationship one with another, whereas no case of myatonia has been reported in the myopathic family.
- (3) A large majority of the cases of myatonia are congenital, the condition

being obvious at birth. In a minority of cases myatonia has appeared acutely and has reached its most severe degree in a few days. In none of its several types is myopathy present at birth, nor does it ever appear acutely or reach its maximum in a few days.

(4) The characteristic muscular flaccidity is not present in myopathy.

(5) The local muscular wasting that is a marked feature of myopathy is not present in myatonia.

(6) The course of myopathy is one of progressive muscular weakness, that of myatonia is one of progressive amelioration of the symptoms.

(7) Return of the deep reflexes after their persistent absence for months or years has been recorded several times in myatonia, and has occurred in two of our cases reported by Collier and Wilson. Such a return of an absent deep reflex has never been recorded in myopathy.

An endeavour will be made to deal with each of these points, and it will be shown that in all points (with the exception of the acute onset of myatonia) these cases correspond to that which may occur in myopathy. It may in the first place be stated that evidence is accumulating to show that typical cases of myotonia do occur rarely as a family disease. Sylvestri has recorded two cases in one family, the first and fifth children, the second and third being healthy, the fourth being a cretin. A maternal aunt suffered from the Landouzy-Déjerine form of myopathy. The elder child at the age of sixteen is said to have presented a typical picture of Erb's juvenile form. Finkelnburg has recorded a case in which three members of a family were affected, although a pathological examination was only obtained in one. One of the cases, D. S., recorded by myself as of the simple atrophic type, had a younger brother similarly affected, although at the time of publication I was ignorant of the fact. These facts dispose of the first two points raised. The third point is based on the statement that in none of its several types is myopathy apparent at birth. It is, however, a well recognized fact that the facial weakness of the Landouzy-Déjerine type of myopathy is a striking feature in early infancy. This feature was present in one of the cases of myatonia recorded by Collier and Wilson.

It is perfectly true that myopathy never arises acutely nor does it reach a maximum in a few days, and any case which presents such symptoms should be subject to the severest criticism and not accepted without a complete pathological examination. If this symptom were common in myatonia it would form one of the greatest objections to the view which regards myatonia as a form of myopathy; but it is a rare manifestation and the cases in which it has been recorded can hardly be taken as proof of its occurrence. That an acute illness may bring into prominence symptoms which have not been observed previously is admitted, but that the true hypotonic condition of the muscles seen in typical cases of Myatonia congenita is acutely produced has not been proved.

With regard to the two further points of distinction between the two conditions, viz. the absence of the characteristic muscular flaccidity of myatonia in cases of myopathy, and the local muscular wasting that is a marked

feature of myopathy, they cannot be held as distinguishing characters, for marked flaccidity is present in many cases of myopathy and localized wasting is by no means always present.

The next point of distinction is important; for if it could be shown that recovery was the rule in cases of myatonia it would be a distinguishing point of some importance; for recovery in cases of myopathy is of most exceptional occurrence (this point will be dealt with in the second section of this article), although arrest of the disease occurs more often.

Now if one examines the recorded cases of *Myatonia congenita*, in *not one* has recovery taken place; as the child develops a certain gain of power has taken place, so that the child may possibly learn to stand or walk in a fashion. In the case D. S., of the simple atrophic form of myopathy already mentioned, who was under my care for some years, the improvement was marked, according to the account given by those who had charge of him, and he was photographed in a standing position with a tennis racquet. As a matter of fact the boy could not stand alone, although he could do so with a little support. In many cases of myatonia the condition has been progressive deterioration, not amelioration.

The final point on which stress is laid is the return of the deep reflexes, which is said never to have been recorded in myopathy. It is a point which shows that improvement in the tone of the muscles has taken place; but such improvement of tone may take place in a myopathic muscle under suitable conditions, and the return of knee-jerks has been recorded by Jendrassik.

The two important clinical points of distinction which would seem to warrant the separation of the group myatonia from the myopathies are (1) that cases of myatonia appear acutely and reach a severe degree of paralysis in a few days; (2) that there is a tendency to recovery.

If it can be shown that these two symptoms are characteristic of the disease and occur in any considerable proportion of the cases then there would be some ground for separating them from the myopathies; but at present there is no such evidence and the pathological evidence, which will be dealt with later, is strongly in support of the view that regards these cases as myopathies. Certain French writers, Mousson and Lévi-Sirugue, whilst admitting that the cardinal features of myopathy are present, yet seem to favour the view of a separate disease on account of the marked hypotonicity of the muscles.

Having adopted the view that these cases described under the title *Myatonia congenita* belong to the great group of the myopathies, there is no need for an elaborate explanation to account for the weakness of the facial muscles seen in some of these cases. Knowing how characteristic a feature is the weakness of the face in the Landouzy-Déjerine type of myopathy, and knowing also that this feature is from time to time found in association with other types, it is not surprising that it should occur in the group *Myatonia congenita*.

Passing over the next three well-known types, the pseudo-hypertrophic, the juvenile, and facio-scapulo-humeral types, the less known distal type has to be considered.

The distal type. The characteristic features of this type are the weakness and atrophy of the distal muscles, while the proximal muscles remain well developed. Although the condition was originally described by Gowers, yet its full recognition and its separation from the peroneal or neuritic muscular atrophy is due to Spiller.

The case which Gowers described was that of a boy aged 18, who when twelve years old was noticed to be weak in his legs, and at a somewhat later date had weakness of the hands. The weakness steadily increased. The muscles for flexion of the foot at the ankle and extension of the toes were small and weak, whilst the movements at the hip and knee were good and powerful. A similar condition was found in the upper limbs. The grasp was feeble, extension of the fingers and wrists was weak, and the muscles of the forearm were small. Above the forearm the muscles had fair power and presented no wasting. In the affected muscles electrical excitability was lowered. The sterno-mastoids were wasted, only a small fasciculus of the sternal part remaining, suggesting rather a congenital defect than an atrophy. Gowers has pointed out this defect in other forms of myopathy. One of the best instances of the distal type of myopathy is that described by Spiller. In this case the disease started in a man aged twenty-six and affected the distal muscles of the legs and arms. After the condition had been present for some years the shoulder muscles were also affected; the patient died ten years later, and on examination of the nervous system no change could be found, but characteristic changes were present in the muscles. Déjerine and Thomas also record a similar case in which the symptoms began when the patient was 49 and lasted for thirty-one years. On examination of the spinal cord and nerves no change could be found. The muscles, however, showed changes similar to those found in myopathy.

Campbell described a form of distal atrophy in three members of a family, the mother and sister of the patient being similarly affected. The patient stated that her own condition, like that of her sister, was congenital, and that, notwithstanding the condition of her feet and hands, she was able to join in games with other children. The patient exhibited a marked degree of atrophy of the muscles of the hands and forearm, and also wasting of the muscles of the leg, especially below the knee, giving rise to a deformity of the foot similar to that seen in Friedreich's disease. There was no alteration of sensation. Although there is presumptive evidence that these cases are myopathic in nature, yet in the absence of a pathological examination it is difficult to state that they may not belong to the peroneal group. Reference should be made here to the familial atrophy of the hand-muscles described by Thompson in seven members of a family in five generations. In what group these cases should be placed must remain doubtful, but they stand in some clinical relationship with the distal type. The difficulty of distinguishing this distal type of myopathy from the peroneal type of muscular atrophy originally described by Chareot, Marie, and Tooth is very great. There is no doubt that this latter disease is a myelopathic affection, as shown by the work of Siemerling, Sainton, and Gierlich, and the observations of Spiller and others show that in the distal type of myopathy

the central nervous system is normal. It is difficult to insist on any one point which can be held to be distinctive; but the affection of peripheral sensation which is often found in the peroneal type would seem to be one point on which stress may be placed. The absence of pronounced contraction of tendons which is a feature in cases of the peroneal group is a point to which in the writer's opinion very little importance can be attached. The presence of deformity depends upon the relative affection of two antagonistic muscles, and if both be equally and simultaneously affected little or no deformity results. Hoffmann accepts involvement of the facial muscles as part of the peroneal type; but the presence of weakness of the facial muscles is so characteristic a feature of the myopathic group that without pathological evidence, which is not forthcoming, one would be inclined to attribute any case in which the weakness of the facial muscles was present to the myopathic group.

It is impossible at the present time to draw any hard and fast line between the distal type of myopathy and the peroneal type of muscular atrophy. There are, however, two points on which some stress may be laid: (1) if there is alteration of sensation in the peripheral portion of the limbs it is a point strongly in favour of the nervous origin of the disease, and (2) if the facial muscles are affected it is a point strongly in favour of the muscular origin of the disease.

Myatonia atrophica. The disease described under this name is one which is characterized by the rare association of muscular atrophy with a slow relaxation of muscles after voluntary contraction. It may well be questioned whether this group should be placed under the title Myopathy. The slow relaxation of muscles after voluntary contraction is the characteristic feature of Myotonia congenita (Thomsen's disease), and some writers—Hoffmann, Steinert, and others—hold the view that these cases should be so regarded. The myotonic features are, however, in many cases very limited in distribution, and occur after the muscular wasting has been present for many years. It must, however, be admitted that the muscular atrophy does in some instances develop in typical cases of Thomsen's disease (Nogues and Sirol). The muscular atrophy has a distribution which is characteristic and has been present in fifteen out of the twenty-seven recorded cases. There is weakness of the face (myopathic face), atrophy of the sterno-mastoids, atrophy of the vasti of the thighs and dorsi-flexors of the feet. The masseter and temporal muscles are sometimes affected, as are also the extensors and flexors of the forearm. The disease tends to affect members of a family in the same generation. Hoffmann described the disease in a brother and sister, Pässler in two brothers, Hunt in two brothers, and Batten and Gibb in two brothers and one sister. The disease occurs in the male sex more frequently than in the female, and in the majority of instances the symptoms manifest themselves between the ages of twenty and thirty, the youngest case on record being fifteen. The disease tends to run a slowly progressive course, and patients are able to continue their work for many years. The distribution of the atrophy in some cases, especially as regards the legs, bears a resemblance to that seen in the distal type of myopathy, and if it is admitted that in that type the

face is sometimes affected the resemblance between the two types is still greater. The pathological evidence as to the nature of this disease is very scanty. There is a record of one post-mortem only, and pathological examination by Steinert, and he found degeneration of the posterior columns of the cord with atrophy of the posterior roots, the anterior roots and the cells of the anterior horn being normal; the muscles showed the changes commonly found in myopathic muscles.

In conclusion to this section of the review the leading points on which it is desired that emphasis should be placed are:—

(1) That the condition described under the title 'Myatonia congenita' should be recognized as a group of the myopathies.

(2) That it is convenient to recognize another group under the title 'Distal muscular atrophy'.

(3) That a further group should be recognized under the title 'Myotonia atrophica'.

If these groups be accepted, then it is possible to allocate most cases of myopathy which come under observation to one of the groups suggested in the beginning of the paper, always remembering, however, that cases will arise which exhibit features characteristic of one or more of the above types. Such cases should be assigned to the type which they most closely resemble, or if it is impossible so to place them they must be relegated to the mixed or transitional type—a group which, with the above classification, will be small and inconsiderable.

II

Does Recovery or Arrest of Disease take place in Cases of Myopathy?

This is a question which it is of the greatest importance to consider. It is recognized that the rapidity with which the disease advances in the different types of myopathy is subject to great variation. The child who is born with a myopathic weakness of the face often shows no other symptoms of the disease till between the second and third decade of life, and even then the disease may make but little or no advance. On the other hand, a child apparently healthy till seven or eight years of age develops signs of pseudo-hypertrophy paralysis which rapidly progresses, so that at the age of fifteen or seventeen he is completely crippled. Oppenheim has stated that improvement occurs in cases of Myatonia congenita, and this has been used as an argument against the condition being related to the myopathies. Oppenheim also describes abortive forms of myopathy in which the shoulder-girdle is affected, and in which there is no tendency for the disease to advance. He records the case of a man aged 30 with this form of weakness which had made no progress since he was ten to twelve years old. The question has lately been raised by a paper published by Marina under the title, 'Gibt es *formes frustes* oder rudimentäre Formen der muskulären Dystrophie, und ist deren Heilung möglich?'

This is followed by a case of muscular dystrophy, published by Erb, and by

a paper by Jendrassik on 'Heilbare Fälle von Muskeldystrophie'. Marina gives as an instance of the late development of the disease, the case of a man aged 31, one of twins, the twin dying immediately after birth. As a child he learnt to talk at two, and to walk at two and a half; but he was always weak and of poor intelligence, and easily tired. He could not do gymnastics and was, owing to weakness, excused military service. The disease remained in abeyance till the age of 30, when after mountaineering it became more pronounced.

Marina's case of recovery was as follows:—A girl aged eight and a half began to suffer from scoliosis; there was no hereditary history, and the mother had had five children and three miscarriages since the last child. The child was always somewhat weakly and tired easily. On physical examination nothing abnormal could be found of the nervous system. A slight scoliosis was present and the scapulae stood out from the trunk. There was atrophy of the supra-spinatus and the upper half of the infra-spinatus, while the lower half was hypertrophied. The serratus and trapezius were very poorly developed. There was also atrophy of the humeral portion of the pectoralis major. The middle portion of the deltoid was abnormally well developed, whilst the other portions were hypertrophied. The musculature of the arms was very poor. If the hand was placed in the axillae the abnormal motility of the shoulders was striking. The gluteal muscles were hypertrophied. The musculature of the lower limbs seemed normal. The gait was natural. The child could get up from the ground well. The knee-jerks were normal. The faradaic irritability of the muscles was diminished. The whole symptom-complex, with almost typical distribution of hypertrophy and atrophy, left little doubt that the case was one of dystrophy. The patient again came under observation when 14 years old, then a well-developed, perfectly healthy girl. The mother stated that her daughter had steadily grown stronger, and that the general and local weakness of the muscles had entirely disappeared. On examination there was a slight scoliosis, and on raising the shoulders there was slight winging of the scapulae. The hypertrophy of the infra-spinatus and the gluteal muscles was still evident. In spite of these features the case may be described as one in which recovery had taken place. Marina then refers to two cases, the one published by Armand-Delille and Weil, of a boy aged 7 in whom the disease had only been present for two months when first seen. The upper and lower extremities were affected, and improvement took place in twelve days! and recovery was complete in February, 1906, the first signs of weakness having been noted in May, 1905.

The second case is that of Lévi and Rothschild, a case of myopathy with lipomatosis, in which improvement took place after treatment with pituitary extract.

Erb, in a communication to Marina, says: 'It is not possible for me to express an opinion on the "formes frustes". I have not seen a case which I could place under that heading. There are certain cases of so-called muscular defects in the pectoralis, serratus, and trapezius which one might call arrested dystrophy; but this opinion is more or less hypothetical. I have seen many

cases in which the disease has become stationary and has not advanced in later life, but only one case of undoubted recovery.'

This case is recorded in the *Münch. Med. Wochenschr.* under the title, 'Ein Fall von geheilter Dystrophia Muscularis Progressiva.' The case was that of an English child aged 7 years, one of a family of three, the other two being quite healthy. For about eighteen months it had been noticed that the child was uncertain in its gait and easily fell, and for the last few months had difficulty in rising from the ground, and within the last few weeks the arms could not be raised without swinging them above the head. The shoulder-girdle was thin and atrophied. In the legs there was nothing especially noticeable, and there was no hypertrophy of the calves; but there was weakness of the flexors of the hip. The oblique muscles of the abdomen were also weak. The electrical excitability in the affected muscles was simply diminished and no reaction of degeneration was present. The deep reflexes were normal and sensation was perfect. The diagnosis of the juvenile form of muscular dystrophy seemed certain. The course of the disease was not, however, what would have been expected; for gradual recovery took place, and when 10 years old the child seemed perfectly healthy. Of the dystrophy there were but the slightest signs. The trapezius was still weak, and the lower portion of the pectoralis and the posterior portion of the deltoid were also weak. The scapulae still winged somewhat, but the raising of the arms was quite good. The serratus and latissimus dorsi were fully restored. Six years later the child was still in good health and perfectly strong.

Jendrassik in 1909 records two cases of recovery: the first, in spite of severe weakness, made an almost complete recovery with the return of reflexes; in the second, a member of a myopathic family, the weakness has become less and less marked.

The first case was that of a girl aged 10, in 1898, the daughter of Jewish parents who were not related. A brother of the patient, three years old, was healthy. The child walked at two years, but often fell. When ten years old it was noticed that the gait became much worse, and on examination there was found loss of the deep reflexes and a flaccid condition of all the limbs and weakness of the extremities. The abdominal and back muscles were weak. The patient could with difficulty raise the arms to the horizontal level. The face muscles were normal. There was no pain or alteration of sensation and no bladder or rectal trouble. The weakness was progressive for some weeks, the thighs wasted, the muscles became very soft, but no fibrillary twitching was observed. The arms were very weak, but the hands were normal and there was no atrophy of the thenar muscles. She remained in this condition for half a year, and then gradual improvement set in. In August, 1899, she had grown fat, she could walk with an unsteady gait, and could get up from the floor with difficulty and with the help of her hands. The muscles had become stronger, the knee-jerks were still absent. In November, 1900, the knee-jerks were still absent: she had made further improvement, but frequently fell when attempting to walk. In June, 1901, the gait was almost normal, the knee-jerks could not be obtained. In

July, 1902, the knee-jerks were obtained with reinforcement, but the Achilles-jerks were still absent. In April, 1904, the knee-jerks were present and she could walk well. In November, 1908, there was still some unsteadiness of the hands, but otherwise she was quite well.

The second case is that of a boy who, when first seen, was aged 12, and suffered from a condition very similar to that with which his uncle and sister were affected. The uncle, now 30 years of age, had always been weak in the legs. This weakness, although present in early life, became marked in the legs when he was 8 years old, and in the arms when 14 years of age. On examination he had weakness and wasting of the upper and lower arm muscles, and to a lesser degree of the lower extremities. There was a marked limitation of the movements of the shoulders, elbow, hip, knee and foot joints. The movements were quite free over a limited range. The cause of the limitation was shortening of the muscles.

The same process was present in the sister of the boy, and she was first seen when 9 years of age; she is now a girl of 18 and in the same condition as her uncle. She can still walk, thanks to many tenotomies; but the gait is shuffling and she often falls. These two cases show the hereditary nature of the disease. In the boy, in spite of the fact that he was three years older than his sister and that the affection began at an earlier age, so that at 6 years old he had had tenotomy performed, the disease had made no advance. The boy when first seen had strikingly thin thighs, and could only raise himself from the lying position with the help of his hands. Two years later the boy could get up more easily and walk much better. Six years later the sister was almost helpless; the boy gets about well, but is not quite normal and he cannot fully extend the left knee. He was, however, passed for military service. He is now 21 years old. The disease in the uncle and sister has advanced, and in the patient it has become less marked.

Criticism. There are in reality two questions to be considered. The first: Do certain forms of myopathy become arrested? The second: Is there any evidence that recovery ever takes place in true myopathy?

With regard to the first question, there is, I think, but little doubt that some cases of myopathy become arrested, and most observers will admit this. The second case above recorded, published by Jendrassik, is a good instance of this, and also of the variability of the disease in different members in the same family.

The second question is the more important and the one on which the evidence must be carefully considered. Of the cases above recorded those of Armand-Delille and Weil and of Lévi and Rothschild may, I think, be at once excluded, the weight of evidence being strongly against accepting them as cases of myopathy. The cases recorded by Marina, Jendrassik, and Erb have then to be considered. With regard to Marina's first case it may be said, it is a case which may fairly be placed in the first group of arrested disease; for it is one in which the symptoms remain latent for many years and only develop after severe exertion. Marina's second case is one which needs most careful consideration,

there is a history of weakness during the whole of life, but the development of lateral curvature when $8\frac{1}{2}$ years of age brought the child under medical observation. It was then found that there was weakness of the muscles of the shoulder-girdle, with atrophy of some and hypertrophy of other muscles. The legs showed no weakness and the deep reflexes were normal. When seen again six years later, the child had almost completely recovered, except for slight scoliosis and for slight winging of the scapulae. This case must, I think, be accepted as a case of myopathy in which recovery had taken place. It is easy to suggest possible errors with regard to diagnosis; but in spite of the fact that the child was not seen for six years, and that no special line of treatment was adopted, I feel inclined myself to admit this as a case of recovered myopathy. In Jendrassik's first case, a girl of 10, there had been life-long weakness of the leg, which had become more pronounced when 10 years old. The child had difficulty in getting up from the floor and had general weakness and wasting of the muscle of the limbs with absence of deep reflexes. Improvement gradually took place, and after four years the knee-jerks returned and she regained good power in the legs. Four years later she was quite well except for some unsteadiness of the hands. In this case again, the evidence for the diagnosis of myopathy might be criticized, yet it is difficult to see in what other group the case could be placed.

With regard to Erb's case the diagnosis can hardly be called in question; the features of the case were those of the juvenile form, and recovery took place in three years and was practically complete in six years. Having carefully considered these three cases it must be admitted there is evidence that myopathy rarely becomes cured. How rare this recovery must be is shown by the experience of Erb, who states when recording the case, 'I have formerly in a wide experience of such cases never seen recovery take place and did not consider it possible, but this case has taught me otherwise.'

III

The Pathology of Myopathy.

The morbid anatomy of the several types of myopathy has been well investigated, and it is generally recognized that in most cases no change can be found in the nervous system, but that the muscles show various degrees of atrophy and fibrosis. There are, however, three types, i. e. Myatonia congenita, Myotonia atrophica, and the distal type in which the morbid anatomy is based on the pathological examination of but one or two cases in each group, and the results of these investigations will be considered. The case on which Landouzy and Déjerine, in 1874, based the description of the type of myopathy which bears their name died in 1902, and the pathological report has been recently published.

Although the statement that in cases of myopathy the nervous system is generally intact whilst the muscles show marked change is in the main true, it

must be borne in mind that changes have been found in the spinal cord in a certain number of cases of muscular dystrophy.

Gordon Holmes, in a typical case of dystrophy, found a considerable diminution in the number of the cells of the chief groups of the ventral horns. The atrophy and diminution in the number of fibres of the ventral roots corresponded to the loss of the ventral horn cells. Similar changes were found in many of the bundles of the nerve trunks. In other cases observed by Erb and Schultze, Heubner, Schutz, Strümpell, Kollarits, Lorenz, Rocaz and Cruchet, Port and Ingbert, there was a similar diminution in the number of ventral horn cells, whilst in the cases reported by Kahler, Fromaier, Preiss, and Sabrazès and Breugues, the cells had undergone atrophy or slow degenerative changes.

It is not easy to decide at once on the origin and significance of the lesions which were found in the lower motor neurons in these cases. Holmes discusses three possible explanations: the first, that the nervous disease is primary and the muscular atrophy secondary to it; secondly, that the neural and muscular changes were the result of coincidence dystrophies; thirdly, that the neural changes were secondary to the primary muscular disease. While admitting the possibility of the first two views, it is the third which appears to be the most probable in these cases. It is well known that reactionary changes can generally be found in some part of the neuron when the muscle in which it terminates has been removed by amputation; but there is no evidence of neural degeneration secondary to disease entirely limited to muscular tissue. It seems very probable that, when muscle fibres undergo complete atrophy and disappear, the functional equilibrium of the neuron which terminates in those fibres must be disturbed, i. e. the terminal branches of the axis cylinders left naked by the disappearance of the muscle fibres will probably be injured and possibly destroyed by the connective tissue which proliferates secondary to the muscular disease.

If these changes in the nervous system are secondary to the muscular disease, why do they occur in some cases of primary myopathy and not in others? It cannot depend on the clinical variety of the disease, for they have been described in the pseudo-hypertrophic type, the juvenile type, and the facio-scapulo-humeral type. Neither does it depend on the age or onset of symptoms or on the duration of the disease. Holmes compares the integrity of the nervous system in some cases of primary muscular atrophy and the atrophy or degeneration of some of the lower motor neurons in other cases to the fact that sometimes all the ventral horn motor cells disappear after amputation of the segment of the limb which they supply, whilst in other cases these cells may be practically unaffected.

One of the most interesting cases of the pathological condition of myopathy recently published is that recorded by Landouzy and Lortat-Jacob. It was the observation of this case in 1874 which enabled Landouzy and Déjerine to identify the facio-scapulo-humeral type which is often known by the conjoint names

of the observers. The patient died in 1902 at the age of 45. The condition was then one of advanced atrophy. In many of the muscles no trace of striation could be detected, and in certain muscles, i. e. the orbicularis oris and palpebrarum, no trace of muscular fibres could be found. The examination of the nervous system was entirely negative, the cells of the ventral horn being perfectly normal. The examination of the bones showed that there was a marked rarefaction of the compact tissue.

In the case of an old woman, aged 80, recorded by Déjerine and Thomas, in whom progressive atrophy of the interosseous muscles of the hand had been observed for thirty years, no change was found in the spinal cord, but the muscles presented changes consistent with a primary myopathic condition.

In Spiller's case of myopathy of the distal type, to which reference has already been made, no change was found in the spinal cord, but the characteristic changes were present in the muscles. Some of the muscle fibres were greatly atrophied, but in others the longitudinal and transverse striation was well preserved.

The morbid anatomy of Myotonia atrophica is based on the examination of portions of excised muscles by Rossolimo and on the full pathological examination by Steinert.

Rossolimo found in the portion of muscle excised a great variation in the size of fibres from 23 to 195 μ . The normal fibres were small in number. The atrophic fibres were rounded or oval, and the connective tissue was increased between the individual and between the bundles of fibres. The sarcolemma nuclei were greatly increased in number and were arranged in chains of varying length. In the case examined by Steinert some degeneration of the posterior columns was found in the lumbar region of the spinal cord, and this could be traced up into the cervical region, where it became limited to the column of Goll. The fibres of the extra-medullary portion of the posterior roots were in the lumbar region considerably atrophied, whilst the anterior roots appeared normal. The cells of the ventral horn were normal, and there was no change in the lateral columns of the cord. The muscles showed the changes which are commonly found in myopathic conditions. That is to say, there was an increase of the connective tissue between the muscle fibres, a simple atrophic degeneration of the muscle fibres, an increase of the fat, and a general cirrhotic condition of the muscle. Steinert discusses the relation of this disease to Thomsen's disease and to myopathy. He holds the view which Hoffmann had already expressed, that these are true cases of Thomsen's disease, and that the myopathy in this particular form is engrafted on to Thomsen's disease. He pays but little attention to the degeneration of the posterior columns of the cord and regards it as an incidental condition. Although this view may be correct, yet if it is shown by the examination of further cases that degeneration of the posterior columns is a constant or frequent feature in the pathology of the disease, the inclusion of this group among the muscular dystrophies will have to be reconsidered. The condition of the muscles, however, is a point strongly in favour of regarding the condition as primarily myopathic.

The pathology of Myatonia congenita is based upon the examination of excised portions of muscle, and upon the complete pathological records of Spiller, Baudouin, and the most recent and most complete record of Collier and Holmes. In Baudouin's case the muscles were largely replaced by fat, and contained a considerable excess of fibrous tissue; the majority of the fibres which remained were atrophied and contained a large number of sarcoplasmic nuclei, but others were enormously hypertrophied and were penetrated by nuclei. There was a relative excess of muscle spindles. The muscular changes were identical with those found in cases of primary muscular dystrophy. The spinal cord was small, and there was possibly a diminution in the number of ventral horn cells and a reduction of the ventral roots. As Holmes points out, the similarity of the histological changes in this case to those found in certain cases of myopathy is undoubted. In Spiller's case again, the central and peripheral parts of the nervous system showed no change, whilst the changes in the muscles were great. In Collier and Holmes's case the following is a description of the muscle changes. A few bundles of normal fibres were found, but the most prominent change was the extreme smallness of the muscle fibres. In the majority of muscles not a single fibre approaching the normal in size could be seen. These small fibres when cut longitudinally were seen to be fairly uniform in character and their cross striation was well preserved. No degeneration or regressive changes could be made out in these small atrophic fibres. A striking feature of the appearance of cross section of muscle was the presence of relatively enormous fibres which measured 100 to 150 μ in diameter. Apart from their size these giant fibres appear to have a normal structure and contained nuclei only immediately under the sarcolemmal sheath. Some of these fibres showed a central nucleus and vacuolation. In longitudinal section a few of these enlarged fibres were splitting up longitudinally into apparently well-formed fibres of small calibre provided with a normal sarcolemmal sheath and nuclei. A considerable thickening of the walls of many of the blood-vessels was a noticeable feature in the sections of the muscles. The peripheral nerves showed but little change, and in the spinal cord the reduction in the number of cells in the ventral horns to about one-third their number was the most striking feature. In considering the relation of the morbid anatomy of these cases to that of the myopathies, the author concludes with the following words: '*On comparing the muscle changes found in these two conditions we must admit that there is no essential difference, though in the younger case there was perhaps not so great an increase of nuclei in the atrophied fibres as is generally present in the myopathies. Myopathic muscles are characterized by the presence of atrophied and hypertrophied fibre, with a proliferation of their sarcoplasmic nuclei and various regressive changes in them, an increase of connective tissue and a disposition of fat, and it is exactly the same changes we record above. Further, we observe a thickening of the vessel walls which is almost constant in the myopathic muscles, and the collection of small round cells which have been referred to are similar to those which may be seen in myopathic muscles.*'

Mention should be made here of the important observations which Bing has made on the pathological condition of the muscles of twelve cases of advanced rickety hypotonia, in which the Hagenbach symptom (i.e. crossing the feet behind the neck) was present. He found an increase of the muscle nuclei, but no fatty infiltration or interstitial change in the muscles.

Bing points out that rickety hypotonia, which in certain clinical features may resemble Myatonia congenita, must not be confused with that disease.

Conclusion.

The object of this article has been to consider the present standpoint of our knowledge with regard to the myopathies or muscular dystrophies.

In addition to the ordinary well-recognized types, viz. the pseudo-hypertrophic, the juvenile, and the facio-scapulo-humeral type, the following types have been added, viz. the simple atrophic type (Myatonia congenita), the distal type, and the Myotonia atrophica type.

It has been shown that the condition described under the title 'Myatonia congenita' is a true myopathy, both on clinical and pathological grounds, and that it should be included in the simple atrophic type, or the name Myatonia congenita might replace the name 'simple atrophic type'.

It has been shown that the distal type is a true myopathy and distinct from the disease described by Charcot, Marie, and Tooth (peroneal type), which is a myelopathic affection and should not be included under the myopathies.

The group Myotonia atrophica has been placed with the myopathies and not with myotonia or with the myelopathic affections, since the evidence, both clinical and pathological, is in favour of such a view: it is admitted, however, that in the only case which has been fully examined pathologically certain changes have been found in the posterior columns of the cord. If in further examinations this is found to be a constant feature it will necessitate the removal of this group from the primary myopathic affections.

It is recognized that there are many cases of myopathy which do not correspond in all particulars to the characteristics of any one type, but may possess the features of two or more types. These should be placed with the type to which they bear the strongest resemblance, or, if that is not possible, in the group of mixed and transitional cases.

The myopathies or muscular dystrophies must be regarded as a whole, and though for clinical purposes it is convenient to separate them into types yet there is no hard and fast line of distinction between one type and another.

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Simple atrophic type of myopathy. The case was shown before the Neurological Society, 1903. It was to this peculiar attitude that the name 'frog-child' was originally applied by Dr. Head. Note the general atrophy of muscles, the long feet and hands, and the position in which the boy 'walked'. He was unable to assume the erect attitude owing to the contraction of the flexors of the thighs and legs.



OCHRONOSIS ASSOCIATED WITH CARBOLURIA

By A. P. BEDDARD

With Plate 10

THERE is a considerable difference of opinion whether there is any causal connexion between carboluria and ochronosis. The following case is of assistance in deciding this question. It will be convenient to describe the case, and then to discuss the connexion between the pigmentation and the carboluria.

Ellen B., married, aged 50, was admitted into Guy's Hospital on October 28, 1909, complaining of general weakness. She had had six children and no miscarriages. Three of her children were alive and healthy; no peculiarity of their urine had been observed. Of the other three children, one died a few hours after birth, one at six months of some acute illness, and one at eight years of scarlatinal nephritis. She was not aware that the urine of any of her relatives had ever been noticed to be peculiar.

Previous medical history. She had never been robust, but had not suffered from any serious disease or ailment. While she was bearing children she developed varicose veins in both legs. In 1891 a small ulcer appeared on the inner aspect of the right leg; it slowly increased in size and had never healed. In 1901 she was admitted into Guy's Hospital; the ulcer was skin-grafted, but soon broke down again. In 1903 the varicose veins in the right leg were operated upon in King's College Hospital; but the ulcer did not heal. In 1904 an ulcer appeared on the left leg and rapidly increased in size. Since the middle of 1905 she had regularly attended the out-patient department for skin diseases at Guy's Hospital. During almost the whole of this period she had applied carbolic oil (1 in 20) to the ulcers; lint was soaked in the oil and kept on the ulcers night and day. The records of the Hospital dispensary show that she was supplied on an average with 6-8 pints of the oil every week. The quantity seemed so enormous that the dispensary authorities suspected that she was selling the oil. They made inquiries, and found that the ulcers were being dressed daily by a nurse and that the whole of the oil was being applied to the ulcers. During July 1907 she was an in-patient in Guy's Hospital for sixteen days. She was admitted for oedema and ulceration of her legs; the ulcers were dressed with carbolic oil; neither abnormal pigmentation about the patient nor any change in her urine were noted. In March 1908 she was again admitted into Guy's Hospital, on this occasion for vomiting. She remained in the Hospital for seventeen days and went out relieved. The symptoms were ascribed to general enteroptosis, from which she was found to be suffering. On admission her urine was noticed to be dark; this was ascribed to carboluria, but there is no record of the tests by which this diagnosis was made. For the first time since 1905 the use of the oil was stopped; and the report of the case notes that her urine ceased to be abnormal. On her discharge from the Hospital she returned to the out-patient department and to the use of the oil, which was continued until the present time.

The patient stated that in March 1908 her friends first noticed a dark discoloration of her eyes and ears. When her attention had been drawn to it she said that she could see it herself; and that it was no more marked than it was previously. This latter statement, however, can hardly be true; because the physician under whose care she was at that time in the Hospital has kindly

looked at her again now, and he tells me that whilst he noticed nothing abnormal about her face in March 1908, it would be impossible now to overlook the pigmentation of her eyes and ears. Therefore it seems probable that the pigmentation was first noticeable after the continuous use of carbolic oil for about three years; and that it had increased considerably during the last eighteen months.

History of the present illness. For several weeks before admission she suffered from a group of symptoms which were new to her, namely extreme drowsiness, vertigo, and tinnitus in both ears. As no local lesion in the ear or elsewhere could be found to account for them, and as they rapidly disappeared when the legs were no longer dressed with the oil, it seems probable that they were due to intoxication with carbolic acid.

Condition on Admission. The patient was a thin woman with dark brown hair and eyes. The circulatory, pulmonary, and nervous systems were normal; general enteroptosis was present. The temperature was normal.

The ulcers completely encircled the legs above the internal malleoli; that on the right leg measured 8 inches vertically, and that on the left leg 6 inches. They were very sensitive to the touch and covered with healthy red granulations which bled readily. The feet were slightly oedematous.

The skin of the face, hands, and whole body was pale, uniform in colour, and no darker than would be expected in a woman with her colouring.

The ears, even when looked at from a distance of several yards, were strikingly blue-black in colour. The pigment was not in the skin; it was uniformly distributed over the concha and antihelix. The lobule and helix were not pigmented.

The eyes were less strikingly pigmented than the ears; but even from the end of the bed the discoloration was very obvious. The pigmentation of the sclerotic consisted in each eye of two triangular dark-brown areas situated laterally. The patches were surrounded by normal sclerotic and were situated about half-way between the edge of the cornea and the inner or outer canthus. On the outer side of each eye there was a small spot of very dark brown pigment situated in the conjunctiva; it was no bigger than a pin's head and was supplied by a very vivid conjunctival blood-vessel. These details are shown satisfactorily in the accompanying plate (Plate 10).

The hands. When the patient made a fist, a faint bluish discoloration of the knuckles could be seen.

No pigmentation could be found in the feet nor about the cartilages of the ribs, the nose, or larynx. The nails and mouth were not pigmented. The ribs and long bones were examined by X-rays, but no abnormal shadows could be seen. No form of chronic arthritis was present.

Treatment. The patient was given a diet of milk. Hot boracic fomentations were applied to the ulcers.

The urine corresponding to the first twelve hours after admission had a sp. gr. 1.014; it was acid and free from albumen. It was of a dull yellow or 'smoky' colour when passed; it darkened to an appreciable extent after standing exposed for a day. The patient was shown this darker urine and recognized that within the last few years, but never before, she had occasionally passed urine of the same colour; but she attached no importance to it. Some of the urine was acidified with hydrochloric acid and steam-distilled; the distillate gave a copious white precipitate with bromine-water, and a red colour with Millon's reagent. The urine reduced Fehling's solution and an ammoniacal silver solution in the cold, but in both cases only to a trifling extent; it gave a slight greenish colour with a dilute solution of ferric chloride. It was therefore clear that the urine contained, in addition to phenols, a small quantity of some substance which might be either hydroquinone or homogentisic acid; it did not contain the chromogen of melanin.

After the first day the urine was no longer 'smoky' and did not darken on exposure; it gave no colour with ferric chloride and did not reduce Fehling's

solution. Three days after admission the distillate from the acidified and steam-distilled urine gave only a trace of a precipitate with bromine-water. In order to exclude the possibility of the patient being a case of partial alkaptonuria, she was then placed on an ordinary mixed diet to which two pints of milk and three ounces of plasmon were added daily. At the end of three days the urine was tested again. It gave no change in colour with a dilute solution of ferric chloride and did not reduce either Fehling's solution with heat or ammoniacal silver solution in the cold. Homogentisic acid was looked for by Garrod's method. 25 grammes of solid neutral lead acetate were dissolved in 500 c.c. of hot urine and then filtered. The filtrate after remaining in a cool place for twenty-four hours showed no crystals of lead homogentisinate; and when tested directly it gave none of the reactions of alkaptonuria. Another portion of the urine was benzoylated according to the method of Orten and Garrod, but yielded an absolutely negative result.

The patient has recently been seen again, that is in March 1910. During the last five months she had not used any carbolic oil. Several specimens of her urine have been tested and not found to show any abnormal reaction. There is a striking diminution of the pigmentation both of the eyes and ears. The same phenomenon was noticed by Reid in his case.

*The Relationship between Ochronosis and Chronic Intoxication
with Carbolic Acid.*

The present case appears to be the twentieth recorded case of ochronosis. Five of these cases, including the present one, have been associated with a prolonged application of carbolic oil to ulcers on the leg. The length of time during which the oil was used, and before the pigmentation was observed, has varied between twenty-four years in Reid's (15) case and three years in the present one; in both cases the strength of the oil was 1 in 20. In Pope's (10), Reid's, and the present case the urine had been noticed to be dark or black at times; this was not so in Pick's case (11), and in Graeffner's (13) the point is not mentioned. In all of them alkaptonuria was almost certainly absent. In regard to the clinical symptoms they have all shown the characteristic pigmentation of the ears and eyes. In Graeffner's case there was in addition some yellowish brown discoloration of the skin of the face; in Pope's and Pick's cases the pigmentation of the skin of the face, neck, and hands reached an extreme degree. These last two cases came to an autopsy and were demonstrated to be genuine ochronosis. It is fair therefore to assume that the other three cases would show the same pigmentation of the cartilages post mortem.

There are six cases on record in which ochronosis has been associated with undoubted alkaptonuria, namely Osler's three cases (7), Ogden's (8) case of alkaptonuria which according to a note in Osler's first paper has developed ochronotic pigmentation of the ears, the case reported by Gross and Allard (14), and that of Van Amstel (16) which was combined with cystinuria. Gross and Allard's case has alone come to an autopsy, which is described in detail by Landois. It proved to be a case of ochronosis; it was peculiar clinically in that there was no pigmentation of the ears, eyes, or skin, but only of the nails of the hands and feet. There are two more cases, namely Albrecht's case (6) and that reported by Clemens (12) and by Wagner (9), which probably belong to this alkaptonuric group. Both were

proved post mortem to have ochronosis; but the abnormal substance in the urine was not demonstrated beyond all doubt to be homogentisic acid.

In Hecker and Wolf's case (4) melanuria and not alkaptonuria was present. In v. Hansemann's case (3), although the urine was black, both melanuria and alkaptonuria appear to have been absent.

In the remaining five cases, namely those of Virchow (1), Bostroem (2), Heile (5) (2 cases), and Wagner, no abnormality in the urine is known. In Wagner's case a specimen of urine was not obtained. The other four cases were published before it was realized that an examination of the urine might throw light on the cause of ochronosis. The urine in these cases was not noticeably abnormal for the very few days during which any of them were under observation, and was therefore not specially tested. In this connexion it must be remembered that the passing of noticeably dark urine is by no means a constant feature in either alkaptonuric or carboluric cases. Thus in Gross and Allard's case the phenomenon disappeared for an interval of fourteen years. Therefore it is not justifiable to assume that this group of four cases necessarily constitutes a special kind of ochronosis merely because the urine was not noticed to look abnormal.

The pigment of ochronosis is unfortunately an amorphous substance and its exact chemical composition is unknown. At least four views have been held about its origin. This difference of opinion is of importance to the point in question, because two of the views would practically exclude the idea that carboluria could have any causal connexion with ochronosis. The earlier observers, Virchow, Bostroem, and Heile, considered that the pigment was haematogenous in origin. This view has been generally abandoned and need not be discussed.

In 1902 Albrecht suggested that alkaptonuria might be the cause of ochronosis. He considered that homogentisic acid or some derivative of it combined with the chondro-mucoid or chondroitin-sulphuric acid of cartilage to form the pigment.

In 1906 Pick put forward a view which, like that of Albrecht, is equally applicable to cases of alkaptonuria and of carboluria. Homogentisic acid is known to be a normal intermediate product of metabolism, and is derived from the tyrosin and phenyl-alanin formed by the disintegration of the proteids in the food and tissues. In alkaptonuria the disruption of these aromatic bodies is carried only as far as homogentisic acid, which therefore appears in the urine. We know that a black pigment is produced when homogentisic acid is slowly oxidized outside the body; and Pick has suggested that the ochronotic pigment is formed in the tissues by the action of ferments. Similarly in cases of chronic intoxication with carbolic acid he believes that the same pigment is produced by the action of similar ferments upon the aromatic oxy-acids formed in the body from phenol. Some of these substances, such as hydroquinone, are closely allied to homogentisic acid, which is hydroquinone acetic acid, and yield a similar black pigment when oxidized outside the body. There can be no doubt that Pick's view offers a satisfactory explanation of how a black pigment might be formed in either carboluric or alkaptonuric patients; but it does not explain why

the pigment is formed and then only in some cases. The latter difficulty applies equally to Albrecht's view. In carboluric cases there must be an absolute increase of aromatic substances introduced into the body; nevertheless it is not obvious why any of this material should be converted into pigment and retained in the body instead of being excreted as aromatic compounds in the urine. It might be suggested that there may be a limit to the power of even a healthy kidney to excrete these substances; and that when this limit is overstepped, aromatic bodies are retained and converted into pigment, which is deposited in the tissues or finding its way into blood is excreted in the urine. On the other hand in alkaptonuria there is no increase of aromatic substances in the body. We know that healthy kidneys can pass out all the homogentisic acid derived from a liberal diet, and that a comparatively small proportion of alkaptonuric patients are known to have developed ochronosis. The frequent association of chronic cardio-vascular disease with ochronosis may be of importance in this connexion. Of the fifteen non-carbolic cases eleven have undergone a careful post-mortem examination; and all of these, with the exception of Albrecht's case, have shown serious cardio-vascular change, as can be seen in the following table:—

Case.	Sex and Age.	Urine.	Arthritis.	Post-mortem appearances.
Virchow	M. 67	Clear	+	Aortic aneurysm, ascites, hydrothorax, oedema of feet and lungs
Bostroem	F. 44	Not mentioned	+	Chronic aortic and mitral endocarditis, old umbilical hernia, acute intestinal obstruction
Heile	F. 36	Not mentioned	0	Mitral stenosis, chronic nephritis, operation for tubal gestation.
Heile	F. 52	No change	0	Mitral stenosis, ulcer of leg
Wagner	F. 67	Not obtained	+	Arterio-sclerosis, chronic aortic and mitral disease, parenchymatous nephritis
v. Hanseemann	M. 41	Black urine for 18 years	0	Dilatation and hypertrophy of heart, aneurysm of left ventricle, general oedema, hydrothorax
Hecker & Wolf	M. 73	Melanuria for 11 years	+	Arterio-sclerosis, granular kidneys, mitral and aortic endocarditis, myocarditis
Gross & Allard	M. 47	Alkaptonuria	+	Aortic valvular disease, kidneys healthy
Clemens	M. 31	? Alkaptonuria	0	Chronic mitral endocarditis, tuberculous pleurisy and peritonitis, general tuberculosis, kidneys tough
Albrecht	?	? Alkaptonuria	0	Tuberculosis of lungs, kidneys, and intestines, heart healthy
Pick	F. 77	Not alkaptonuria	+	Aortic and mitral endocarditis, myocarditis, coronary atheroma, atrophy of both kidneys

Landois is inclined to look upon the cardio-vascular changes, like the arthritis, as a result of alkaptonuria. But whether they are or not, there is a possibility that by interfering with renal excretion they may help to produce a retention of aromatic substances in the body which may gradually be deposited as ochronotic pigment. Pick's carbolic case showed similar changes.

Pick's view has been adopted by Garrod and by other observers. Recently, however, several writers have disputed its correctness, and especially that part of it which suggests a causal connexion between carbolic acid and ochronosis.

Wagner, whilst admitting the possible correctness of Pick's view, believes that the pigment is a complex nitrogenous substance. He points out that homogentisic acid and the oxy-acids derived from phenol are simple non-nitrogenous bodies; and that these could be converted into such a pigment only by a process of synthesis and condensation, which are not likely to take place in the tissues. He therefore considers that neither alkaptonuria nor carboluria can be the direct cause of ochronosis; but that alkaptonuria and ochronosis are two closely allied but independent conditions, which possibly have the same anomaly of metabolism as their common cause. There are, however, several considerations which can be urged against this view. In the first place it is based on the chemical examination of an amorphous substance obtained from cartilage. It is therefore extremely unlikely that the pigment has been obtained in such a state of purity as to warrant one drawing any far-reaching conclusions from its analysis. In the second place, since Albrecht suggested in 1902 that alkaptonuria might be the cause of ochronosis, the fourteen recorded cases, with one exception, have been associated either with alkaptonuria or the use of carbolic acid. The exception is Wagner's case, in which no urine was obtained for examination. In the third place Gross and Allard claim to have produced ochronotic pigmentation by placing normal cartilage into a solution of pure homogentisic acid. Unfortunately they give no details of their experiments, and in the absence of confirmation no great stress can be laid upon them.

Gross and Allard believe that all cases of ochronosis are due to alkaptonuria. They raise two objections to Pick's view that intoxication with carbolic acid does produce the condition. In the first place, although they admit that from a chemical point of view carbolic acid might cause the pigmentation, they object that in Pope's, Pick's, and Graeffner's cases—the only ones known to them—the examination of the urine was incomplete and did not exclude alkaptonuria. They state that alkaptonuric urine no longer reduces copper solutions when it has turned black on exposure; and that its dark colour would hide any reduction even if the oxidation were incomplete. This objection might apply to Pope's case. But Pick expressly states that the urine in his case did not darken and that it gave no reduction with Trommer's test. Alkaptonuria is said by Graeffner to have been excluded in his case; and in Reid's case and the present one it was certainly not present. In the second place, they point out that no case of ochronosis was reported between Virchow's case in 1866 and Bostroem's in 1891; and that during these years the use of carbolic acid as a general antiseptic was

prevalent. This argument, however, has a double edge and might be used just as well to prove that alkaptonuria cannot be the cause of ochronosis. The obvious explanation is that the condition was not generally recognized either during life or post mortem until several cases had been reported. Consequently Pope's case, which was observed in 1895 and considered to be an anomalous case of Addison's disease, was left unpublished for eleven years. It was recognized as ochronosis as a result of the publication of Osler's cases in 1904, which were the first to be diagnosed during life.

Landois draws two sweeping conclusions from Gross and Allard's experimental production of ochronosis. The experiments are considered first to disprove Pick's view that carbolic acid can produce ochronotic pigmentation, and secondly to prove that all cases of ochronosis must be due to alkaptonuria. In answer, it is only necessary to point out that even if the experiments do show that homogentisic acid can produce the pigmentation, they do not prove either that hydroquinone cannot or that no substance other than homogentisic acid can.

Van Amstel's objections are different. On the one hand he admits that when ochronosis is associated with alkaptonuria, the homogentisic acid impregnating the cartilages is somehow converted into the pigment. But, on the other hand, he concludes that it is 'extremely unlikely that ochronosis should result from a prolonged application of carbolic oil to open wounds'. The only grounds for this belief which I can find in his paper are contained on p. 200. There he repeats Wagner's objection that hydroquinone is too simple a body to be converted into so complex a substance as melanin; but he quite forgets, which Wagner did not, that this argument is equally fatal to the derivation of the pigment from homogentisic acid. On the same page he also repeats Gross and Allard's objection that the use of carbolic acid is common and cases of ochronosis are rare.

The carbolic cases of ochronosis are now too numerous either to be ignored or to be ascribed to coincidence. Writers who disbelieve Pick's view in regard to them have to explain them away somehow. Landois, Gross, and Allard suggest that they are really alkaptonuric cases; this is certainly untenable now. Van Amstel believes that they are of the same nature as Virchow's case. This moribund patient was under observation only for two days before death; the urine was clear, but was apparently never tested. Consequently no one can ever know the true nature of the case. Van Amstel, however, comes forward with an explanation of this and the carbolic cases. He points out that theoretically no chemical conversion can be absolutely complete within finite time; and that therefore it is impossible for all the homogentisic acid formed in the body to be oxidized even in normal people. He believes that these minute quantities of the acid circulating in the body can blacken the cartilages, and will do so in the course of time, provided that the patient is predisposed to ochronosis. He does not enlighten us further about this predisposition. It is not obvious that by calling an unknown factor predisposition he satisfactorily explains either why ochronosis is not universal or why it ever occurs.

A review of the most recent cases of ochronosis only confirms Garrod's conclusion 'that whereas the nature and origin of the urinary pigmentation in some cases of ochronosis remain obscure, there is good reason to believe that in one group of cases the ochronosis is due to the metabolic error which is known as alkaptonuria, and in another has its origin in the local application of carbolic acid extending over many years'. It can also be stated that there is just as good evidence, both clinical and post mortem, that ochronosis is caused by carbolic acid as by homogentisic acid; and from a purely chemical point of view the probability of the connexion is the same in the two cases.

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Manuscript

BIGEMINY OF THE VENTRICLE AND AURICULAR FIBRILLATION

By THOMAS LEWIS

(From the Medical School, University College Hospital¹)

With Plate 11

IN a recent paper (Lewis) it has been shown that the complete irregularity of the heart, which is met with so commonly as an accompaniment of degeneration of that organ, and *a fortiori* in heart affections which are a sequel of rheumatic fever or chorea, is the result of fibrillation of the auricle. The view is held that the normal rhythm production of the sinus is in abeyance and that an irritable auricle is elaborating and discharging impulses in many parts of its musculature. The contraction waves generated at several or many foci are colliding and the auricle, as a whole, is in a state of inco-ordination or delirium.

Now it is well known that if one auricle is thrown into the fibrillary state experimentally, the other follows suit. The same phenomenon is observed in fibrillation of the ventricle. A limited portion of the intact auricular or ventricular tissue cannot be maintained in fibrillation; the condition spreads and involves either the whole auricle or the whole ventricle. Yet it is well known that fibrillation is never transmitted as such from auricle to ventricle or from ventricle to auricle. When the auricle is fibrillating the ventricle responds to the impulses received from it in an irregular but nevertheless co-ordinate manner. When the ventricle fibrillates the auricle beats likewise arrhythmically, but with co-ordination of the separate contractions. These phenomena suggest that fibrillation can spread from one area to an adjacent area only when the bridge of tissue which effects the union between them is so constituted and arranged that it may participate in the process. The auriculo-ventricular bundle, which, as Fredericq's transection experiment has shown, transmits the impulses from auricle to ventricle while the former is in delirium, is sharply defined on all sides. Continuity of the musculature is established at the terminations of the junctional tissues above and below, and at these points alone. Consequently while the auricle fibrillates, the bundle transmits certain of those impulses only which are showered promiscuously upon the small area abutting upon the upper termination (the node of Tawara). Contraction waves flowing in several directions towards the narrowing channel which forms the impulse-inlet to the

¹ This paper is based upon observations made under the tenure of a 'Beit Memorial Fellowship'.

[Q. J. M., July, 1910.]

ventricle are eventually transmitted in a single direction (along the usual path), and confusion of impulse transmission in the bundle itself is avoided. From the turmoil in the auricle a rapid and haphazard succession of waves escape, and escaping, are confined to a single course the boundaries of which are parallel. Thus two facts are explained: first, the absolute irregularity of the ventricular responses to a fibrillating auricle, and second, the inability of the fibrillation to transmit itself from upper to lower chamber or *vice versa*.

But regarded in this way, and assuming the function of the junctional tissues to be perfect, it will be obvious that when auricular fibrillation is present it is almost if not quite inconceivable that the ventricle should beat regularly in response to impulses generated in a chamber in which the inco-ordination is of a high grade.² Nevertheless, and in the condition considered, it not infrequently happens that certain of the pauses preceding pulse or heart beats are of constant length.

A state of accurate coupling of ventricular beats may occur, and is a frequent result of the administration of drugs of the digitalis series. This coupling is illustrated by the accompanying figures (Plate 11) and has been referred to in previous communications. It is of a curious nature, for while the distance between large and small beats is constant, that between small and large beats shows the same want of regulation as does the usual or uncoupled rhythm. The reason for the accurate spacing between large and small beats must be sought. We have the choice of two alternatives. The ventricular contractions may originate in auricular impulses alone, or they may not. Now if the ventricular contractions are shown to emanate from auricle alone, then we have either to admit the proposition of the presence of auricular fibrillation to be false, or else to modify our conception of the abnormal mechanism very considerably. If on the other hand it can be shown that the beat which is preceded by an inconstant pause (the larger one) arises in the auricle, while that which is preceded by a constant interval (the smaller one) is intrinsically ventricular in origin, the position is not only clear, but an additional support, if such is necessary, is lent to the proposition that the auricle is in a state of fibrillation.

The ventricular electric complex of the normal beat is characterized in its opening phases by a quick movement in the base-negative direction (upwards in the figures). The direction and shape of this peak (R) are indications of the supraventricular origin of the ventricular contractions. If in a curve composed in the main of individual ventricular complexes of the normal type we meet with other complexes of a divergent type, we may conclude that the last have

² Were the inco-ordination less it might be possible that an irregularity might result in the ventricle, which recurred periodically; thus we might be led to anticipate, under such circumstances, an occasional or a rhythmic duplication of a particular period of irregularity. Such repetition is not encountered in the abnormal mechanism considered, and we are therefore forced to assume that the generation of impulses proceeds in a highly disorderly and changing fashion.

arisen in a different manner. Now the electro-cardiographic curves which are obtained from patients with complete irregularity of the heart exhibit individual complexes which are for the most part normal in general outline. That is to say, the electric complexes pronounce the supraventricular derivation of the contractions represented. It also happens that other types may be mixed with them. These divergent types are preceded by shortened pauses, and are always absolutely or relatively abortive in their efforts to raise the arterial pressure. This inefficiency of the ventricular beat is in accord with the assumption that it arises at an abnormal point and travels through the musculature of the actual arterial pump in an abnormal direction. The divergent type of beat is usually scattered at irregular intervals along the curves, but when more frequent it may occur after each beat of normal type and at such times may produce the picture of accurate coupling previously mentioned.

In all, I have met with four cases of complete irregularity of the heart in which this coupling was present and in which electro-cardiographic curves were obtained; two of these were examples of accurate coupling in the absence of drug administration; the remaining two, which are used as illustrations, arose as a result of digitalis poisoning.

Figs. 1 and 2 were taken from a girl, aged 22, giving a past history of chorea and admitted to hospital suffering from advanced mitral stenosis with engorgement of the liver and dropsy of the legs. The heart rate on admission was 140 and the beats succeeded each other without rhythm. Digitalis in doses of αx of the tincture was administered three times daily for ten days, and the heart rate fell to 60-40. At this time bigeminy was often present. The dosage was reduced to αv . The heart rate increased slightly but the bigeminy continued. Figs. 1 and 2 were taken on the last day of the digitalis administration, or seventeen days after admission. Fig. 1 is a polygraph curve tracing in which venous and radial curves are shown. The central cycles of the figure belong to a period of bigeminy, and the earlier and later ones to the complete irregularity in its uncomplicated state. The venous pulse is of the ventricular form. Each of the larger beats in the radial curve is accompanied by two systolic waves in the jugular curve. The smaller beats of the bigeminy are represented by single waves in the jugular curve. The distinction between strong and weak beats is even clearer in the electric curve (Fig. 2). The beat which is preceded by the longer or inconstant pause is of the usual type; the complex starts with a peak R directed in the base-negative direction and of short duration. The beat which follows and corresponds to the smaller radial pulsation is of a divergent type. Superimposed upon the whole curve are numerous rapid oscillations, the result of auricular fibrillation (oscillations also appear upon the venous curve). The mechanism with which we have to deal is therefore perfectly apparent. The auricle is fibrillating,³ and each alternate beat of the bigeminy is the result of an irregular auricular impulse. The beats of auricular origin are followed at

³ The oscillations were maximal when the electrodes were placed over those portions of the chest-wall covering the right or superficial auricle.

a constant time interval by beats of intrinsic ventricular origin, for they conform to a type recognized as the outcome of single ventricular extra-systoles interrupting an otherwise normal rhythm. With the cessation of digitalis the heart rate quickened and the bigeminy no longer appeared.

Figs. 3 and 4 are two strips from a continuous curve. They were obtained from a case, the detailed history of which has been recorded in another place (*Heart*, 1909-10, i, Case 11, p. 329). The patient, a young man with mitral stenosis, first came under observation with an irregular pulse as a result of auricular extra-systoles. Electro-cardiograms were obtained while he was in this condition. At a later date the heart's action became completely irregular and further records with the special chest leads were secured. On digitalis the ventricle always showed marked slowing. On the last occasion of its administration the heart rate fell from 180 to 70 and the slower action was accompanied by the appearance of bigeminy. The digitalis was discontinued, but the bigeminy persisted until the curves (Figs. 3 and 4) were obtained (a period of seven days). The first curve, Fig. 3, demonstrates a type of extra-systole of the ventricle which is more readily identified than that of Fig. 2 as emanating from the *left* ventricle. Only a short strip of curve intervened between Figs. 3 and 4, yet the type of divergent beat has altered, though the spacing of the couples, $\frac{2.6}{5}$ sec., remains constant. The extra-systolic contraction in this instance (Fig. 4) approaches a type of beat, yielded experimentally in the dog, by stimulation of the right ventricle at a point not far distant from the middle of the interventricular furrow and on the anterior surface.

We have seen that in two cases of complete irregularity of the heart, in which from time to time phases of accurate coupling or bigeminy were prominent, the mechanism is attributable to the alternate response of the ventricle to impulses derived from auricle and ventricle respectively. The figures are taken from cases actually or recently under the influence of digitalis. The bigeminy seen in similar cases in the absence of drug administration are of an essentially similar nature. The beats preceded by the constant or shortened pauses are of a divergent type.

The accurate coupling which occurs in complete irregularity of the heart cannot therefore be regarded as an argument in opposition to the proposition that the auricle is fibrillating, for the accurate coupling of extra-systoles of the ventricle to the beats which they succeed is a well-recognized phenomenon. It has been suggested that the first beat is actually the cause of the second. This view is supported by the constancy of the pause, and is further evidenced by such an instance as that shown in Figs. 3 and 4, where without alteration in its time relationship to the preceding beat the divergent type of beat arises now from left and now from right ventricle.

The proposition of auricular fibrillation has led to a surmise that the second beats of a couple would prove to be of intrinsic ventricular origin, and

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the confirmation of this surmise is but another argument in favour of the proposition which led to it.

Summary.

The ventricular bigeminy which occurs in clinical instances of auricular fibrillation, either spontaneously or in the wake of digitalis administration, is due to disturbance of the irregular series of responses to auricle, by ectopic beats arising in the ventricular musculature itself.

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EXPLANATION OF FIGURES.

FIG. 1 ($\times \frac{8.5}{12.25}$ linear). Polygraph curve from a clinical case of auricular fibrillation. The first half of the curve shows the bigeminy. The venous curve is of the ventricular form throughout. Some small oscillations, *ff*, are seen from place to place.

FIG. 2 ($\times \frac{8.5}{12.5}$ linear). Electro-cardiogram from the same case. The pauses between the beats are marked in $\frac{1}{2}$ sec. Each alternate beat is of the divergent form, and arises as an ectopic ventricular beat. The oscillations from the fibrillating auricle are well seen. The leads were from right arm and left leg in this and the succeeding figures.

FIGS. 3 and 4 ($\times \frac{8.5}{12.5}$ linear). Two similar curves from a different case. They were taken within a few seconds of each other. They are accompanied by radial curves. In Fig. 3 the divergent type of ventricular complex corresponds to that of an extra-systole of the left ventricle. In Fig. 4 it corresponds to that of an extra-systole from the right ventricle. The spacing of the couples remains constant in the two figures.



FIG. 1



FIG. 2

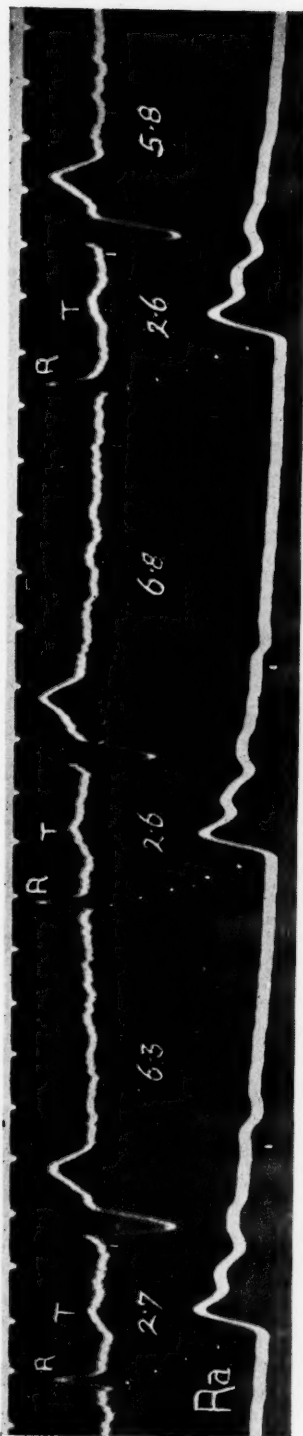


FIG. 3

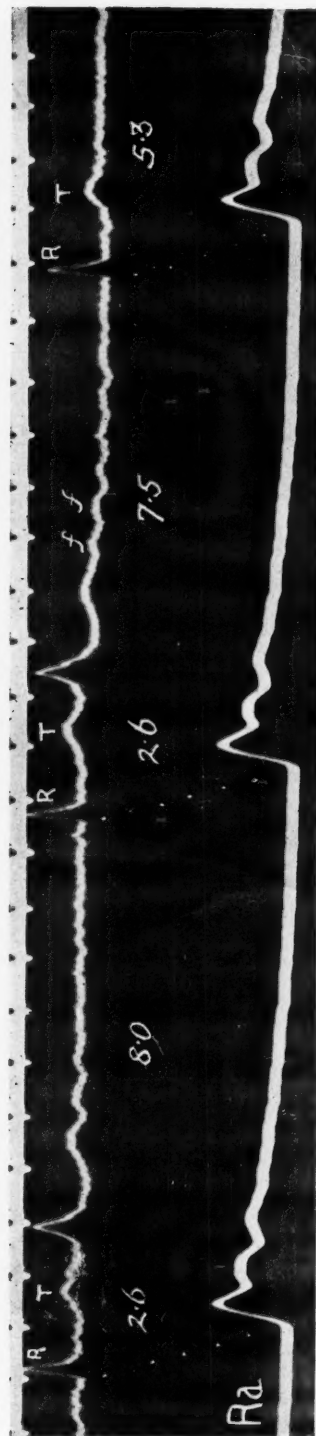
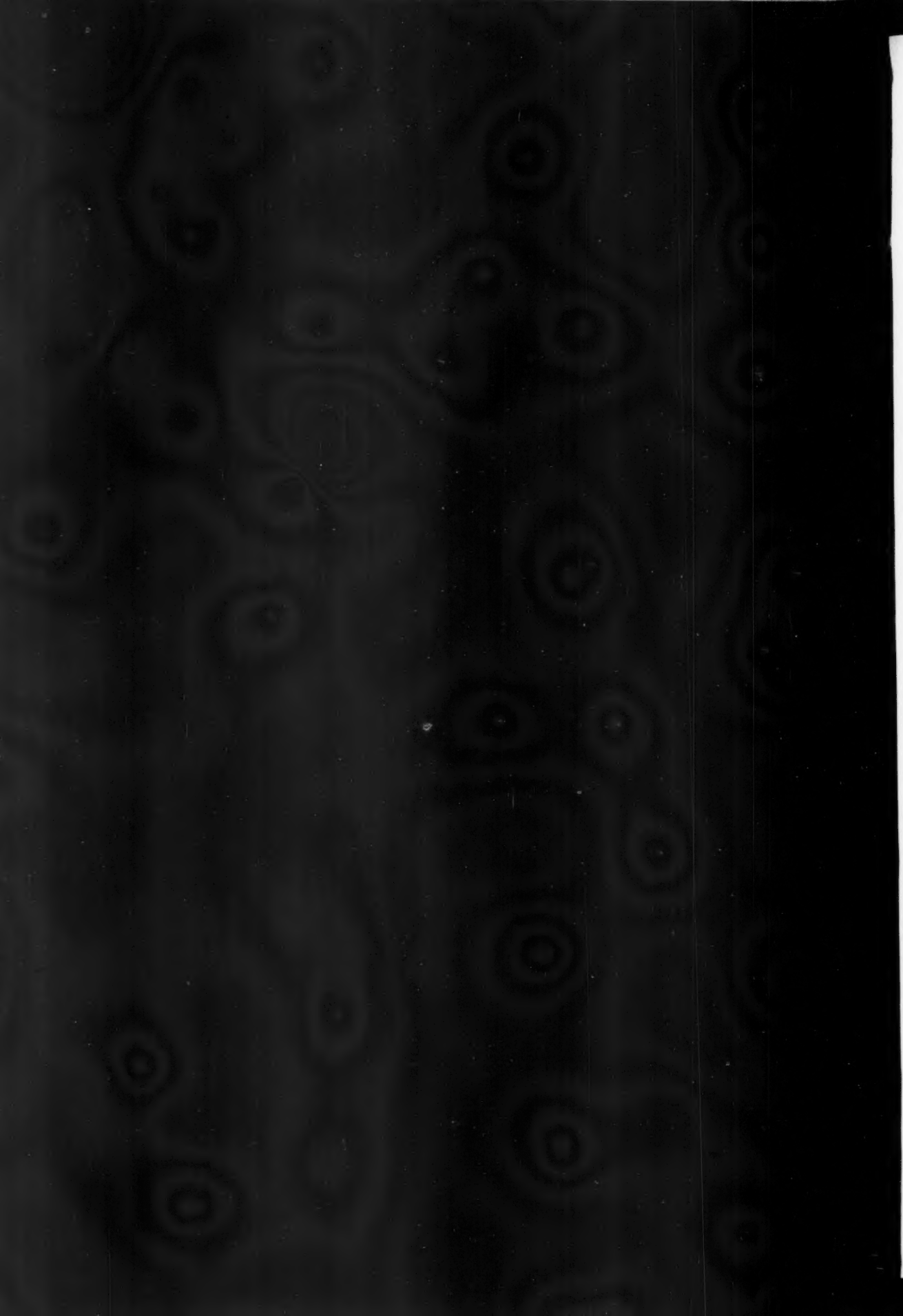


FIG. 4



A SIMPLE CLINICAL METHOD TO DEMONSTRATE AND MEASURE DYSERGIA

By TOM A. WILLIAMS

By dysergia we mean the lack of harmonious co-operation between the agonist and antagonist muscles required to perform a movement steadily and in the direction desired. This disorder may proceed from lack of information as to the position of the various joints participating in the movement; or it may be due to want of knowledge of the degree of contraction of some or all of the muscles concerned both before and during the act. This condition, however, is spoken of as ataxia.

When, however, the movements are unsteady or unmeasured on account of the irregularity or incompleteness of the efferent nerve impulses which govern the muscles concerned, we speak of the affection as dysergia or dysmetria.

Ataxia can be compensated for by the use of other senses than that of attitude. Thus the locomotor disorder of *tabes dorsalis* can be largely overcome by practice under the direction of vision. By this means a new set of muscle-habits is learned which makes use of the scanty information to be derived from the diminished attitude-sense of the patient. The Fraenkel treatment depends upon this principle.

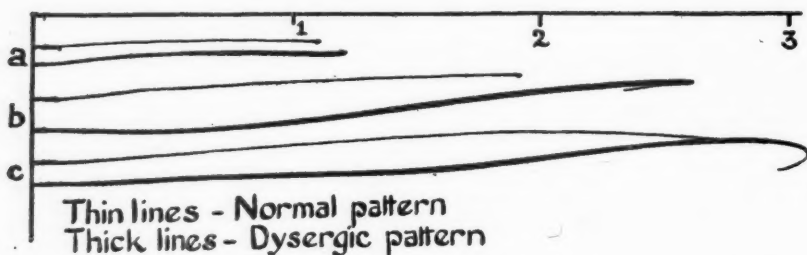
The dysergic patient, on the contrary, does not appear to be re-educable, as far as present information goes.

Thus the diagnosis between these two conditions is one of great practical importance; and not only so, but a quantitative estimation of dysergia should afford valuable information as to the progress for better or worse of the disease which causes the dysergia.

Accordingly, the following method should be of clinical service in these respects. It depends upon the fact that when a dysmetric patient endeavours abruptly to arrest any movement he has begun, he can neither do so nor prevent an excessive movement from occurring in the reverse direction.

So that when the patient, in drawing a straight line, tries to arrest the movement at a fixed point, he will be unable to do so, the pencil travelling beyond. A practical application of this test is as follows:—A horizontal line is drawn across a piece of paper. A perpendicular is let down from its left extremity. Three vertical marks, (1) (2) (3), are made at equal distances along the horizontal line. The patient is then directed to draw, beginning at the vertical line, three horizontal lines, (a) (b) (c), one below the other, and to make

each stop abruptly at the marks (1) (2) (3) respectively. They must be drawn rapidly, and each with a single movement. The normal person will pass the limit only very slightly, and will make hardly any returning stroke or movement of the arm. Cerebellar dysergia is indicated by excessive length, and especially by a too great movement of recovery *whether the paper is marked or not* (see Figure); for the patient may instinctively lift the hand.



A patient with ataxia is usually able to arrest the movement near the desired place, or, if not, the line is an irregular or trembling one.

The quantitative estimation is made by adding together the lengths of the three lines made on the paper during the return movement of the pencil after the patient has arrested the line he is directed to draw. The sum of these lines can then be compared with the sum of three lines drawn later in the course of the case and with the figures drawn in other cases. The method is thus a means of clinical comparison, and is useful in case histories.

The patient from whom the charts are taken suffers only from dysmetria and asthenia. The latter is due to the intensity of the efforts required to compensate for his dysergia in using a type-writer and in walking. I believe that the cause of his disease is sclerosis of the cerebellum, due to arterial thrombi the result of severe malaria; for he has been in this condition for eleven years with only slightly increased impairment recently, and there are no other signs of intracranial disease to lead one to suspect a neoplasm. It is right to add, however, that paraesthesiae of the hands and feet are present. Some physicians believe him to have tabes dorsalis: but dysdiadochokinesis and the above sign show that the symptoms are cerebellar.

MODERN ENGLISH CARDIO-VASCULAR TEACHING

By E. M. BROCKBANK

(Acknowledgement is made for kind permission to use the following figures: Dr. Lewis and Messrs. Shaw & Sons for Figs. 1 and 3, Dr. Mackenzie and Messrs. Macmillan & Co. for Figs. 2 and 8, Dr. Mackenzie for Figs. 4, 5, 7, 12, 14, 15, 16, Dr. Lewis for Fig. 6, Dr. Wardrop Griffith for Figs. 9 and 10, and Dr. Hay for Figs. 11, 13, 17.)

IN this paper will be considered some of the teachings of the modern English school of cardiology, which has in recent years done so much good work under the leadership of Dr. James Mackenzie in studying, by means of venous pulse tracings, the action of the heart both in health and disease. Mackenzie, in the preface to the second edition of his classical work on 'Diseases of the Heart', points out specially that the numerous tracings which he reproduces in the book are most valuable as representing actual facts as recorded by the movements of the heart and blood-vessels. His interpretation of these tracings represents the present state of his knowledge, but he keeps an open mind and is prepared for the interpretations to be modified by the discovery of new facts. Following Mackenzie's line of observation much good work has been done by other investigators, who have fully illustrated their papers by figures. As it seems to a careful reader that many of the deductions drawn by these observers from the facts (i.e. tracings) which they publish are either not clearly explained or else are disputable, it is time to take stock of our knowledge of cardio-vascular conditions and phenomena.

I have accordingly ventured to review some of the work of prominent observers, and have been much assisted in this by receiving the ready permission of these writers to reproduce figures from their publications with which to illustrate my criticism. I wish to take this early opportunity of thanking Doctors Mackenzie, Hay, Lewis, and Wardrop Griffith for this courtesy. As the subject is a very large one, most of my criticism will be directed to the teaching associated with disease of the auriculo-ventricular orifices of the heart.

The points which will be considered are—

I. Conductivity of stimuli through the *a-v* bundle, and the duration of auricular systole;

II. The variation in length of the interval of time which elapses between the onset of auricular systole and the carotid pulse, that is, the *a-c* interval.

III. The so-called nodal rhythm of the heart, i.e. that in certain conditions the ventricular systole precedes auricular systole.

IV. The theory that the crescendo murmur of mitral stenosis is auricular systolic in origin.

Every one of these doctrines is so closely dependent for its proof on the accuracy of the others that if one be disproved all the others become uncertain; but the most vital of all is the doctrine that the crescendo murmur is of auricular systolic origin. It is on the indisputability of this point that much of modern cardiological teaching depends. As the proofs of the above doctrines are so closely related and interdependent, some overlapping will be unavoidable in discussing them.

I. *The Conductivity of Stimuli from Auricle to Ventricle through the a-v Bundle, and the Duration of Auricular Systole.*

As the arguments used to support the teaching on both points are so closely connected, the two questions must be discussed together.

Normally the stimulus for the contraction of the ventricle arises at the sino-auricular node, passes probably along the muscle of the auricle during its contraction to the a-v node, and then through the a-v bundle to the ventricles. There is a definite time occupied by the passage of stimuli through the a-v bundle, and it is taught, as a deduction from jugular pulse records, that this period of time varies considerably in mitral stenosis. This conclusion is arrived at by observations on the interval of time which elapses between the appearance of the a and c waves on the jugular tracing, that is, the a-c interval. This is normally 0.20 sec. in a heart beating slowly, 60-70 per minute.

Mackenzie writes of the a-c interval (p. 170): 'This interval is occupied by three events, namely, (1) the systole of the auricle; (2) the transmission of the stimulus from auricle to ventricle; (3) a minute portion of time during which the ventricular pressure is rising before opening the semilunar valves (presphygmic¹ interval).

'As 3 is practically constant it may for the purpose of this inquiry be ignored, and, assuming that the stimulus for contraction starts on its way to the ventricle at the beginning of auricular systole, *any variation in the length of the a-c interval is due to the variation of the rate of stimulus conduction.*'² In normal hearts I have found that the a-c interval is fairly constant, lasting usually one-fifth of a second. It is a little shorter in frequent action of the heart.'

Mackenzie, therefore, looks upon the presphygmic interval and the rate of transmission of the pulse wave from the aortic valve to the carotid artery as constant; but what his views are as to the duration of auricular systole, whether this is also constant or variable, is not at all clear. As I understand it, however, the argument means that this is constant, and such belief is borne out by Hay's account of the a-c interval in his book to which Dr. Mackenzie wrote an introduction.

¹ 'Prosfygmie' is the correct spelling, but usage is again favouring the adoption of a hybrid word.

² The italics are mine.—E. M. B.

Hay writes as follows (p. 131):—

'The *a-c* interval includes—

- (1) The duration of the systole of the auricle (A);
- (2) The time taken for transmission along the *a-v* bundle from auricle to ventricle;
- (3) The period elapsing between the beginning of ventricular systole and the opening of the aortic valves—the presphygmic interval (B).
- (4) The time taken for the pulse to travel from the ventricle to the carotid artery in the neck at the point where the receiver is placed (C).

(1), (3), and (4) are practically constant; variations in the length of the *a-c* interval must therefore denote differences in the rate of passage of the stimulus from the auricle to the ventricle, that is, variation in the conducting power of the *a-v* bundle. When conductivity is normal the *a-c* interval remains fairly constantly about one-fifth of a second, even in a frequently acting heart. Sometimes, however, in a rapidly acting heart the *a-c* interval is shortened, the reason being that with increase of stimulus production there has been a simultaneous increase in the conducting power of the *a-v* bundle. When the conducting power of the bundle becomes depressed the transmission of the stimulus is correspondingly delayed until the *a-c* interval is double or treble its normal duration.'

The time elapsing between the beginning of the ventricular systole and the appearance of the carotid pulse in the neck is about one-tenth of a second; therefore Hay must allow a similar time for auricular systole and the conduction of stimuli along the *a-v* bundle.

All the above periods of time are calculated for a heart beating about 75 per minute or 0.8 sec. for each beat.

Let us examine these statements as to 'constants' in some detail.

(A.) *Duration of auricular systole.*

It is said that auricular systole begins 0.1 sec. before ventricular systole (Mackenzie), part of which time is occupied, apparently, not by active contraction, but by the passage of stimuli from auricle to ventricle. Physiology has taught for some time that there is a slight interval between the end of auricular systole and the beginning of ventricular systole. This transmission-of-stimulus period is important in view of its possible variation in certain conditions. The actual duration of auricular systole according to Lewis's diagram³ is about 0.1 sec., and Mackenzie adopts a similar period of time in the diagram from Frey which he figures in his book.

The duration of the presphygmic interval in Lewis's diagram is 0.05 sec., and the time occupied by the passage of the pulse wave from the aortic valve to the carotid artery is 0.03 sec. Mackenzie puts the latter time at 0.02 sec., and in Frey's diagram the presphygmic interval is 0.1 sec. Hay allows 0.1 sec. for the presphygmic interval plus the carotid pulse wave, and therefore the duration of auricular systole with stimulus conduction must also be 0.1 sec. No definite time is allotted to the transmission of the stimulus from auricle to ventricle in the normal duration of the *a-c* interval (0.2 sec.) by any one of these writers, but it is said by Hay, and it is suggested by Mackenzie, to be the only

³ *Further Advances in Physiology*, Lond., 1909, p. 88.

variable factor in this interval, and to increase in duration in certain conditions, especially in mitral disease. We are therefore taught now that *auricular systole, the presphygmic interval, and the carotid wave rate* are '*practically*' constant, no matter what the pulse rate be.

Let us see what such a doctrine leads to by taking an example: A heart beating at the rate of 60 per minute occupies 1.0 sec. for its whole cycle, and one beating 'frequently' at 150 occupies 0.4 sec. Now, the period of the cardiac cycle in both these hearts between the commencement of auricular systole and the throb in the carotid artery may occupy 0.20 sec. (it is only 'sometimes' (Hay) that it is shorter than this, and then solely on account of quicker stimulus conduction), therefore the rest of the cycle occupies in the slow heart 0.8 sec. and in the quick heart 0.2 sec. In other words, the quick heart for the first part of its cycle beats at the same pace as the slow heart, and for the rest of its cycle at four times the rate of the slow heart. Further, no matter whether a heart is beating at 60 or 150 beats per minute, there is no difference in the time occupied by auricular systole; nor in that between the onset of ventricular systole and the carotid throb. The ventricles for the first part of their systole, i.e. during their presphygmic phase, contract at an equal rate (although the quick heart is acting two and a half times as rapidly as the slow heart), and therefore for the rest of their systole the ventricles of the quick heart must work four times as rapidly as those of the slowly beating heart to 'keep time', thus making a very sudden change of speed of contraction during its systole.

As no qualification is made to the statement that (1) the auricular systole, (2) the presphygmic portion of ventricular systole, and (3) the rate of the pulse wave from the aortic valve to the carotid artery are constant, we may take a further case of a heart beating at 185 per minute, or only 0.33 sec. for each pulse-beat (Lewis's case—see later on). Here, although the *a-c* interval is slightly less than in the 60-beats heart, it is only because of *quicker conduction of stimuli* from auricle to ventricle; the duration of (1) auricular systole (0.1 sec.), (2) of the first part of ventricular systole, and the carotid wave rate (0.08 sec.) remain constant, and therefore the *a-c* interval occupies 0.18 sec. at least, and the rest of the cardiac cycle 0.15 sec. So the quick heart for its *a-c* interval occupies practically the same time as the slow heart does, and for the rest of its cardiac cycle only about one-fifth of the time taken by the slow heart.

At the risk of being accused of labouring the point I should like to show clearly how this theory works out as regards the ventricle. Normally ventricular systole occupies 0.3 sec. as compared with 0.5 sec. occupied by diastole in a heart-beat of 0.8 sec. duration. Of the 0.3 sec. occupied by ventricular systole, 0.05 sec. is taken up by the presphygmic interval and 0.25 by the rest of the systole; that is, as 1:5. In a heart-beat of, say, 0.32 sec., the normal duration of ventricular systole and ventricular diastole would be three-eighths to five-eighths, i.e. 0.12 to 0.20 sec., though ventricular systole would probably occupy less time, for in a quick heart ventricular systole usually occupies a relatively less amount of time than does ventricular diastole as compared with

the normal rates. We will take it, however, at 0.12 sec. Of this 0.12 sec. the presphygmic interval being constant occupies 0.05 and the rest of the systole 0.07; that is, instead of the former being one-fifth of the latter it is almost equal. This striking condition of affairs is the logical conclusion to the theory that in health the duration of auricular systole and the presphygmic phase of ventricular systole are constant.

That this teaching is really meant is seen from Fig. 1 (Fig. 1) in Lewis's paper on 'Paroxysmal Tachycardia'. Here are jugular and radial pulse records from a patient with a pulse rate of 187, and it is said that the *a-c* interval was equal to or slightly more than 0.20 sec.—certainly it measures this by the time marks. It will be seen that the *a* wave is very prominent, and if perpendiculars be drawn from its origin and from its summit they will be found to enclose a space equal to full 0.20 sec. So here we have a figure showing that out of 0.3 sec. occupied by the whole of the cardiac cycle, not only does the *a-c* interval equal 0.2 sec. or more, but auricular systole itself extends throughout the whole of this period of time, and that is more than twice the time that is occupied by

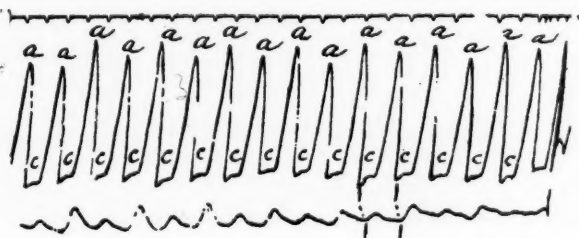


FIG. 1. The time intervals in all the figures are 0.2 secs.

ventricular systole. In other words, whilst the duration of ventricular systole is normally about three times as long as auricular systole, here it is half as long, or one-sixth of its normal relative duration as compared with auricular systole.

The duration of auricular systole as seen in phlebograms. If the duration of auricular systole is constant we ought to find proof of this in all jugular pulse records, for the distance between the perpendicular lines drawn through the origin of a wave due to auricular systole and through its summit ought always to measure 0.08 or 0.1 sec. If we examine carefully the normal jugular pulse records of hearts beating about 60 to the minute we find that the distance between these perpendiculars is covered by a distance equal to an interval of time of about 0.1 sec.

Diminished auricular systole. It is difficult to measure the lengths of *a* waves in rapidly acting hearts taken on slowly moving recorders with time intervals of 0.2 sec. If, however, we take such a tracing as Fig. 71 in Mackenzie's book (Fig. 2), of a pulse of 164 per minute, and measure the 'very minute *a-c* interval', we find that the distance between the line drawn to indicate the onset of auricular systole and the summit of the *a* wave is well under 0.1 sec. The whole *a-c* interval marked on the figure measures about 0.15 sec., and as

the presphygmic-plus-carotid interval is constant and occupies 0.08 sec. there can only be left 0.07 sec. for auricular systole. Some of the *a-c* intervals *altogether* do not occupy 0.08 sec. of time.

This is the only tracing in the book of the jugular pulse in a quick action in which the *a* wave is differentiated. Again, if the tracings of a case of paroxysmal tachycardia published by Lewis in *Heart* be studied it will be seen that the *a* waves are frequently much less than 0.1 of a second in their whole duration, and therefore auricular systole cannot have occupied more than 0.03 to 0.05 sec. Such points can easily be seen in Figs. 6, 7a, 7b, 13, and 14, the last of which is reproduced here (Fig. 3). In these cases the pulse rate was 150-180 per minute.

Increased duration of auricular systole. When we examine the records in which an abnormal heart is acting at a moderate rate, and in which the interval of time between the onset of auricular systole and the carotid wave (normal duration 0.20 sec.) is increased, we find the condition of affairs easier

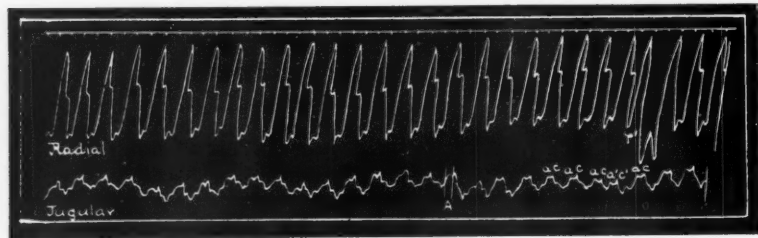
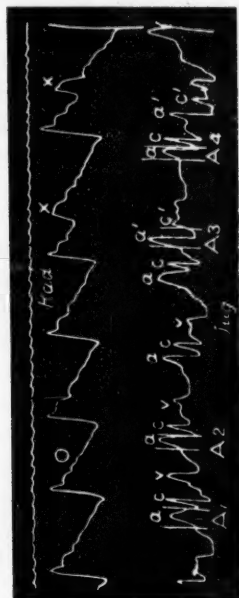
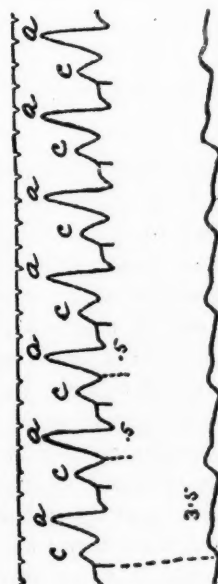
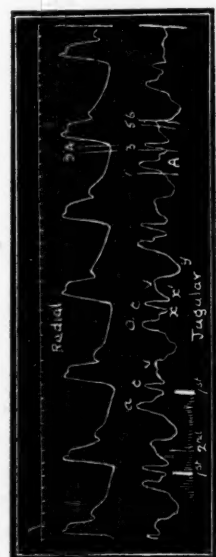
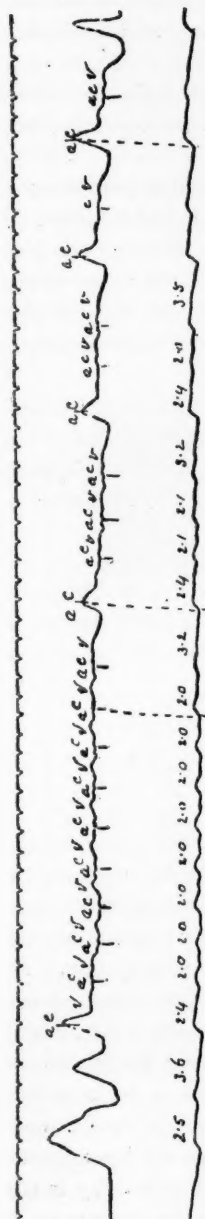


FIG. 2.

to measure. In those cases of mitral stenosis, not under the influence of digitalis, with increased *a-c* intervals which have time intervals recorded, and which have the *a* wave rightly indicated, we find the distance from the onset to the summit of the *a* wave to be often as long as at least 0.15 sec. This is so in tracings shown by Mackenzie; taking the time marked as indicating the onset of auricular systole, in Fig. 112 (Fig. 4) the space marked *A*, and in Fig. 161 *A* (Fig. 5). But it is especially well marked in the tracings used by Lewis to illustrate a paper on 'Irregular Action of the Heart in Mitral Stenosis, &c.' In these tracings the distance between the perpendiculars is often almost equal to that of a time-beat, 0.20 sec.; almost all the waves in Fig. 6 (Fig. 6) show this; and it is even more than 0.2 in some of the waves marked *A* in Fig. 7 (e. g. *A* 16 = 0.25 sec.). In the other figures there are many waves marked *A* which denote contraction on the part of the auricle for 0.15 of a sec. instead of 0.1; in fact the very first *A* wave in Fig. 1 is practically 0.20 sec. from onset to summit. In Mackenzie's Fig. 98 (Fig. 7) the distance between the perpendiculars of onset and summit of the wave due to auricular systole measures 0.18 sec. in the space *A*₁, that is, almost the whole time of the normal *a-c* interval.



If the above measurements are right, it follows that the duration of auricular systole is not constant, but may vary considerably both ways from 0.03 to 0.18 sec., and that consequently all the deductions as to variations in the rate of conductivity of stimuli which are dependent on the supposed constancy of auricular systole are disputable.

(B) and (C). *The duration of the presphygmie interval and the time which elapses between the opening of the semilunar valves and the carotid waves of the phlebogram.*

These two phenomena are also stated to be constant, and I have already referred to the improbability of the presphygmie interval being unaltered in a normal heart which beats at varying degrees of rapidity. The time occupied by the pulse wave travelling the short distance from the aortic valve to the subclavian or carotid artery (whichever, if either, is responsible for the production of the *c* wave) may vary but little in the different rates of heart-beat and may be ignored.

Phlebograms and cardiograms taken on slowly moving recording surfaces afford no satisfactory evidence either way and need not be considered; but Weiss and Joachim have shown that there is a distinct delay in the presphygmie interval in cases of mitral regurgitation of from 0.04 to 0.07 sec. according to the condition of the valve and the heart muscle.

In concluding this section I submit that whether the tracings used to prove the increase of the *a-c* interval actually do or do not prove this point, they show clearly that the observers had no proof that the duration of the auricular systole is constant.

II. *The Prolongation of the a-c Interval in Auriculo-ventricular Valve Disease.*

The theory of the prolongation of the *a-c* interval in mitral valve disease seems to be based very largely, if not entirely, on the assumption that the crescendo murmur is synchronous with auricular systole,⁴ and that disappearance of the murmur in a case means of necessity, with occasional exceptions, complete disappearance of any wave in the jugular pulse due to auricular systole. In these cases of supposed prolonged *a-c* interval it seems as if no measurement were made from the ordinates, as in the calculation of the duration of the normal *a-c* interval, to locate the *a* wave, the observer simply drawing his line where he thinks it ought to go. As a matter of theory, there ought to be, in mitral regurgitation, a delay in the development of sufficient intra-ventricular force to open the aortic valve owing to blood slipping back through the incompetent mitral valve at the earliest part of ventricular systole. With this delay in the presphygmie interval there will be a corresponding delay in the appearance of the carotid pulse, and therefore an increase in the whole of the *a-c* interval. So

⁴ The reasons advanced in support of this contention are considered on a later page.

theoretically we expect a prolongation of the *a-c* interval in mitral incompetence, and Weiss and Joachim show by their cardiographic tracings that such a prolongation does take place and may measure 0.04 to 0.07 sec.

When we examine the tracings which are used to prove this delayed *a-c* interval and measure them carefully, as in the investigation of ordinary jugular tracings, we find that the observer has either overlooked or ignored a wave at the proper position in relation to the radial pulse that the wave should occupy. True, the wave is not always a very prominent one, but then this is only to be expected if the auricle is weak and distended in mitral or tricuspid disease, as is so often the case, and unable to contract with a normal degree of vigour.

An excellent illustration of the ignoring of waves at the proper time for a wave is Fig. 3 from an article on 'The Physics of the Circulation', by Sherrington and Mackenzie (Fig. 8). The *a-c* interval here, as marked, is nearly three-fifths of a second in duration, but why the waves marked *a* have

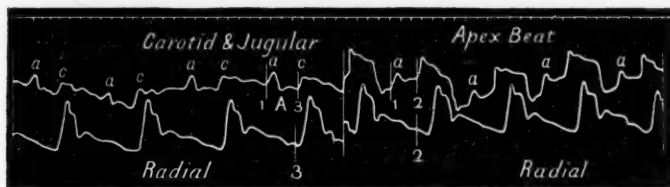


FIG. 8.

been so chosen is not stated. It will be seen that there are distinct waves in the carotid and jugular pulse tracing after those marked *a* and much nearer the proper time for auricular systole. Also in the apex-beat curve there is evidence of a wave after that marked *a* in the first and third beats which could be due to auricular systole.

Another case, interesting also from a different point of view, is Mackenzie's Fig. 161 (Fig. 5), a case of mitral stenosis. The *a-c* interval here is marked as being 0.40 sec. long instead of 0.20 sec. If, however, the figure be examined carefully, especially as regards the last three jugular waves marked *a*, it will be seen that they are compound, and that a wave quite possibly of auricular systolic origin begins distinctly later than the wave chosen. This period of time is, I suggest, made up of 0.30 sec. correction from the radial pulse, with an additional 0.05 sec. for the delay of the presphygmie and carotid wave interval due to regurgitation through an incompetent mitral valve. The line marked to signify the onset of auricular systole is 0.15 sec. at least too early. As I measure it the *a-c* interval in this tracing is about 0.25 sec. If the line marked to indicate the onset of the *a* wave is correct the distance between it and the top of the wave, that is, the duration of auricular systole, is 0.20 sec., that is, 0.1 sec. more than the constant time for this.

Another illustration of the passing over of waves which, occurring at the proper time, are possibly, if not probably, due to auricular systole, occurs in

a paper by Lewis in this Journal on 'Irregular Action of the Heart in Mitral Stenosis and the inception of Ventricular Rhythm'. In Figs. 6 and 7 the wave marked *a* and attributed to auricular systole, without any obvious reason, is, I suggest, wrongly marked. In Fig. 6 (Fig. 6) there is a distinct wave at the proper time for that due to auricular systole and following, by as much as 0.30 sec. in some beats, the wave attributed in the tracing to auricular systole. In Fig. 7 again the wave marked *a* precedes by 0.25 sec. a distinct wave at the proper time for auricular systole.

The case which provided the clinical observations on which this paper of Lewis's is based was one of mitral stenosis in which a crescendo murmur, present at one time, disappeared, but with its disappearance a wave due to auricular systole persisted. It is said to be one of the indisputable facts of modern cardiology that a crescendo murmur is due, in part at least, to auricular systole, and that if no crescendo murmur be heard there cannot possibly be any auricular

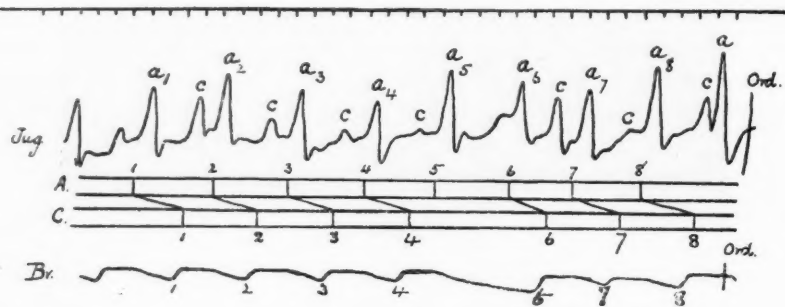


FIG. 9.

systole. As the auricles contract together, if a crescendo murmur disappears there can be no contraction of the left or right auricle, and consequently no wave is seen in the jugular pulse. In Lewis's case he did find a wave, which he attributed to right auricular systole, and yet no contraction of the left auricle was taking place—there being no crescendo murmur; so that the case was reported as being interesting because the left auricle was paralysed and the right auricle still contracting.

Again, Wardrop Griffith publishes a case showing a greatly lengthened *a-c* interval in which similar criticism can be made, a wave being picked out, without any obvious reason, as being due to auricular systole, occurring 0.5 sec. or more before the carotid wave (Fig. 9). Here also there are indications of feeble auricular systole at the proper time, that is, between the termination of the waves marked *a* and the onset of those marked *c*. In most of these pulse-beats there is a distinct attempt at a wave. Why should it be ignored?

Griffith supports his reading of this pulse tracing by the fourth radial beat, which covers apparently two jugular beats. It will be noticed, however, that in the jugular pulse immediately preceding wave *a*6 there is a prominent wave,

apparently identical in character with waves marked *c* in other venous pulse-beats, which is unmarked. It could not be due to a carotid pulse, as there was no systole of the heart to cause it. How is this wave to be explained if Griffith's reading of the other waves is correct?

It may be said that some of the waves which I point out as occurring at the proper time for that due to auricular systole, and which are not taken into account in the proving of the nodal rhythm theory, are due to errors in tracing from the original sphygmograms the figures used in Mackenzie's and Hay's books, as I am informed by Hay was done. The waves are, however, generally too distinct for error on the part of such careful workers; moreover, such a contention cuts both ways, and I may say that possibly some faint indications of waves due to auricular systole which may have occurred in the original tracings were not reproduced in the pulse-beats in which they do not appear in the figures under consideration. It would have been more definite evidence for scientific purposes if actual photographic reproductions from the original tracings had been used.

Some of the tracings in question when rightly measured show, however, that there is a prolongation beyond the normal duration of 0.20 sec. of the *a-c* interval. This can be accounted for, as I have already mentioned, by the delay in the presphygmie interval which occurs in mitral regurgitation, as shown by Weiss and Joachim's work.

Decrease in the a-c interval. Tracings which I referred to in considering the duration of auricular systole show that the *a-c* interval may be considerably shorter than 0.20 sec. It seems a justifiable conclusion, then, that the *a-c* interval may vary considerably in slowly or rapidly beating hearts with mitral valve disease from 0.08 to 0.35 sec., but not because of variations of rate of conductivity of stimuli alone, if at all; therefore, any theories on the supposed variations of conductivity in mitral stenosis which are based on the assumption of an increase in the *a-c* interval are of very doubtful value.

Effect of this new teaching, if correct. Let us assume, however, that these observers have chosen the right wave to indicate the occurrence of auricular systole, and that the *a-c* interval is as prolonged as they assert. What does their teaching mean? It will be well, first of all, in this place to review the physiology of the normal heart cycle, and this can be done by extracts from the article on 'The Physics of the Circulation' written for clinicians by Sherrington and Mackenzie. 'The heart's contraction starts normally at the mouths of the veins and sweeps over the auricles and ventricles. There is a perceptible interval between the beginning of the auricular and the beginning of the ventricular contraction, but no interval can be detected between the contraction of the veins and of the auricles' (p. 1).

In a heart beating 75 per minute and each beat occupying 0.8 sec.—

Systole of the auricle occupies about or less than	0.1 sec.
" " ventricle " " "	0.3 sec.

Diastole of auricle and ventricle, neither contracting, passive interval	0.4 sec.
Diastole of ventricle, including relaxation and filling, up to the beginning of ventricular systole (p. 11).	0.5 sec.

There is no definite time allotted to stimulus conduction by these writers.

'The discharge of its contents by the auricle into the quiescent and already partly-filled ventricle somewhat stretches the slack walls of this latter, and, whether by eddy or otherwise, the valve-flaps are raised toward each other and toward the auricular opening' (p. 4).

Flack writes: 'The chief function of the right auricle is, however, to expel the blood into the right ventricle at the end of joint diastole, and thereby place its walls on a certain tension. The greater this degree of tension the more powerful the contraction.'

There is nothing very new in these statements; they bear out what physiology has taught for some time as to the sequence and relation to each other of the events of a cardiac cycle, namely, that the active part of the cycle (excluding the onset of the contraction at the sinus venosus) begins with auricular systole, which lasts for about 0.1 sec.; during this event or after, or most likely both during and after it, the stimulus to contract is passing through the *a-v* bundle to the ventricle; then ventricular systole takes place and occupies 0.3 sec.; finally ventricular diastole ensues and lasts for 0.5 sec., the first 0.4 of this being a joint diastole with the auricle. An important point here is the duration of the time allowed for rest of each element in the cycle—that of the auricle is seven times as long as its activity, that of the *a-v* bundle about the same proportion, whilst the ventricle's rest to its activity is as 5 to 3.

Now, it is obvious that if the time of stimulus conduction is increased, the increase must occur before the onset of ventricular systole, and we must have a rearrangement of the sequence and relation to each other of, or of the time occupied by, the events of the cardiac cycle. Here we have two alternatives:—

1. The cycle runs its normal course, beginning with auricular systole, accompanied and followed by the *a-v* conduction, then ventricular systole, and ending with the joint auricular and ventricular diastole. In such a case, the increased time occupied by stimulus conduction must be at the expense of that occupied by ventricular systole and the joint diastole, and I have not seen any statement in Mackenzie's or Hay's account of delayed conductivity to the effect that this is not intended. But a short examination of a concrete case will show that this is quite impossible. Let us take Griffith's patient. Here the pulse rate was 115 per minute, Fig. 24 (Fig. 10), that is, 0.52 sec. for each beat. The time occupied between the onset of auricular systole and the carotid wave was 0.46 sec.; therefore, if the increased conductivity took place at the expense of ventricular systole and joint diastole, we should only have 0.06 sec. left for ventricular systole after the carotid pulse and for joint diastole. This is manifestly impossible. In other cases also in which there was delayed conductivity, though

to a less degree, the increase could not have taken place at the expense of the ventricular systole and joint diastole.

2. The cycle is of an abnormal type, auricular systole taking place before the end of ventricular diastole, and even during ventricular systole. If ventricular systole and ventricular diastole are to occupy their proper share of the time of each heart-beat, the delay in conductivity must push auricular systole away from ventricular systole further and further according to the increased duration of conductivity; or, in other words, auricular systole must begin its contraction sufficiently soon before the ventricle is ready to contract again to allow for the delay of conducting through the *a-v* bundle. This means a dissociation of auricular and ventricular cycles, each having a cycle of its own. Again, let us take a concrete case to examine the meaning of this abnormal state of affairs, and Griffith's tracings may be considered, as in them the theory

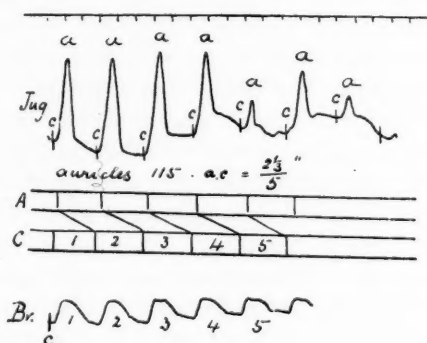


FIG. 10.

of delayed conductivity is pushed to a further degree than in any others that I have met with. The tracing was taken whilst the patient was under the influence of amyl nitrite, but this apparently had no effect on the supposed condition of the *a-v* bundle. Here is a heart beating 115 per minute (Fig. 10), that is, each beat occupies 0.52 sec. The *a-c* interval occupied 0.46 sec. (two and one-third fifths of a second). (A few beats later, in another tracing of his paper, the *a-c* interval was 0.55 sec. out of a total 0.6 sec.) Of this 0.46 sec. the time occupied by the presphygmic interval and the pulse wave to the carotid artery was at most 0.08 sec., therefore ventricular systole began 0.38 sec. after the onset of auricular systole. Conductivity is supposed to begin with the onset of auricular systole. It therefore occupied 0.38 of a sec. out of a total pulse-beat of 0.52, and was accordingly conducting for 0.38 sec. and resting for 0.14 sec., that is, nearly three of work to one of rest. Now, normally the period of conductivity beginning from the onset of auricular systole is about 0.1 sec., which is the constant and unvariable duration (according to the modern teaching) of auricular systole. Therefore in a normal pulse occupying 0.52 sec. the *a-v* bundle is resting at least four times as long as it is conducting. If we assume that conductivity

only began after the cessation of auricular systole, and that it is scarcely measurable in health (?0.02 sec.), the differences between the relative duration of activity and rest of the *a-v* bundle in health and in the case under consideration would be immensely more marked. So in the diseased heart the *a-v* bundle is working at least twelve times as long relatively as it does in the normal heart.

It should also be noted in this case that, as Griffith sees himself, the stimulus begins its passage of the *a-v* bundle in the earliest part of ventricular diastole or even during ventricular systole. Flack, writing of the 'refractory period' of the heart muscle, says, 'If a stimulus be applied to the rhythmically beating ventricle just before or during systole it is without any visible effect. The heart muscle is therefore said to possess "a refractory period", and the possession of this property explains the inability to tetanize it. If, however, the stimulus be applied during diastole, a contraction is produced which is known as an "extra systole". Such extra systoles are followed by a longer pause than usual. This is called the compensatory pause.' If the passage of the *a-v* bundle in this case were uninterrupted and got through to the ventricle during ventricular diastole we should therefore expect to find extra systoles, and as a matter of fact they do occur in some of the tracings, with an *a* wave in the jugular pulse at the proper distance, 0.30 sec. from their origin. This suggests that whilst the conductivity was what one may call hopelessly bad for most of the time of observation it was at times quite good. This is hardly consistent with a chronically diseased condition.

Effect of auricular systole remote from ventricular systole on the latter. There is another important result of the increased delay in conductivity, namely, the effect of auricular systole so early as it is said it may be on ventricular systole. If the auricle contracts so much before the ventricle as it is said to do, our idea of the use of the former in the final distension of the ventricle to induce forcible contraction must be abandoned in these cases. Auricular systole has always seemed to me to be a most important factor in bringing about a proper distension of the left ventricle, which leads to a right degree of force in contraction, and, incidentally, by regulating the load of the ventricle, promotes regularity of the heart's action. I have always looked upon the irregular pulse of mitral obstruction as being due, in part at any rate, to incomplete distension and irregular loading of the ventricle which results from the obstruction of the valve preventing the proper filling of the ventricle, especially when the auricle is unable to contract and add to the final distension. If Griffith's explanation of the tracings is right we must look upon the auricle and ventricle as working independently, each with a cycle of its own, and upon the auricle as neglecting its *chief function* of completing the final distension of the ventricle.

The work of Gaskell on 'The Contraction of Cardiac Muscle' is used as a foundation for not a little of the modern cardiology, and therefore it is very important to remember what he actually made out from his experiments on the heart, which are quoted frequently. Thus Mackenzie writes: 'From Gaskell's experiments we know that if the bridge of the muscle connecting the

auricle and ventricle be narrowed the stimulus takes longer in passing.' What Gaskell says in his article in Schäfer's 'Textbook of Physiology', which is the reference given by Mackenzie, is that if the *auricle* be slit up almost into two parts, one connected with the sinus (*As*), and the other with the ventricle (*Av*), leaving a sufficiently narrow bridge of *auricular muscle* as connexion between the two halves of the auricle, then if *As* be stimulated a delay may occur at the bridge before *Av* contracts, distinctly comparable to and resembling the normal pause which takes place at the *a-v* junction between the contraction of *Av* and the ventricle. This is rather different from Mackenzie's reading of the observations, for in the latter the *a-v* bundle tissue is concerned, in the former, auricular muscle; and the normal pause at the *a-v* junction is reproduced, not an abnormal pause. Moreover, Gaskell shows that if the block in the auricular tissue becomes more marked, there is not a longer delay of stimulus passage but the passage only of every other or every third or fourth contraction. Gaskell further states that a precisely similar experiment can be performed on the frog by means of the screw-clamp in the *a-v* groove. According to the tightness of the clamp the ventricle can be made to beat synchronously with the auricles, to respond to every second contraction of the auricles, to respond to every third, fourth, or other contraction, or to remain quiescent. Here, it must be noted, there is no mention of abnormal delay between the contraction of the auricle and the ventricle, simply no response at all on the part of the ventricle to certain auricular contractions.

Furthermore, Gaskell writes of this 'half-rhythm': 'When each impulse is inefficient to cause a contraction of the ventricle, the ventricular muscle has the power of summing up the effects of two or more of these inefficient impulses, and so continues to beat rhythmically though no longer synchronously with every impulse. The most satisfactory explanation of the summation process is that every impulse which is inefficient to produce a muscular contraction increases the excitability of the muscle and therefore makes it easier for a second similar impulse to cause a contraction.' If we substitute in the above passage the excitability of the *a-v* bundle for the excitability of the ventricle muscle, we bring the explanation into line with modern observations on the *a-v* bundle and explain those cases of true heart-block in which the ventricle only responds to every second, third, or further contraction of the auricle. Such cases undoubtedly exist, but there is no definite clinical evidence to show that the *a-v* bundle ever passes on stimuli at a pathologically slow rate, let alone at such an abnormally slow rate as it is said to do in Griffith's and Lewis's cases.

A prolongation to a certain degree of the *a-c* interval in hearts beating slowly, 60 or 40 or less, is quite conceivable in cases of mitral stenosis or disease of the *a-v* bundle, without there being any alteration at all in the normal sequence of events of a cardiac cycle. By this I mean that auricular systole in a heart-beat of more than 1.0 to 2.0 sec. duration may occur at the end of ventricular diastole, take a little longer time over its systole, be more deliberate or more complete, when it is hypertrophied and has the obstruction of the stenosed

valve to overcome. Cushny states that after digitalis in medicinal doses the rhythm of the auricle is slow like that of the ventricle, owing to inhibition; the relaxation is little changed, but owing to muscular action the contraction is more complete. In this way the *a-c* interval could be prolonged without any physiological difficulty. If we measure the pulse tracings taken from cases of slow pulse due to mitral disease under digitalis, and disease of the *a-v* bundle, we find that the *a-c* interval very often does not exceed 0.40 sec. when the time of the whole pulse-beat is 2.0 secs. Also in one tracing of extreme bradycardia in

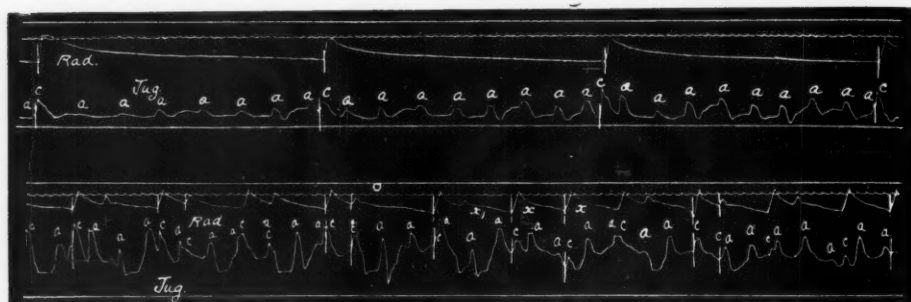


FIG. 11.

which there are about eight auricular beats to one ventricular beat (which occupies about 35 fifths of a second), the *a-c* interval is 0.30 to 0.40 sec. (Hay's Fig. 97) (Fig. 11). In a previous figure (Fig. 96) from the same patient, with the rhythm 2:1 and 3:1, Hay estimates a prolonged *a-c* interval for two of the beats, but this is done by ignoring waves at the proper time for auricular systole which could have been caused by the contraction of the auricle.

For the above reasons, I submit that the evidence regarding the delay of conduction of stimuli through the *a-v* bundle is not convincing.

III. Nodal Rhythm.

The term 'nodal rhythm' is applied by Mackenzie, its originator, to that action of the heart where the 'auricles and ventricles contract simultaneously—the ventricular contraction preceding the auricular by about one-tenth of a second in the great majority of cases'. The starting-place for the stimulus of contraction is believed to be the *a-v* node, not the sino-auricular node. This means that the onset of auricular systole, instead of commencing 0.1 sec. before, may be 0.1 sec. after that of ventricular systole.

The clinical evidence which supports this doctrine of nodal rhythm consists in the disappearance of all signs of auricular systole occurring at the normal

period of the cardiac cycle. Such signs of normal auricular activity are thus detailed:—

1. A wave in the jugular pulse-tracing due to a contraction of the right auricle.
2. A wave in the apex tracing due to the contraction of the left auricle.
3. A wave in the liver pulse due to a contraction of the right auricle.
4. A presystolic mitral murmur due to a contraction of the left auricle.
5. A presystolic tricuspid murmur due to a contraction of the right auricle.

1. Disappearance of a wave in the jugular pulse tracing due to a contraction of the right auricle. The wave in the normal jugular pulse which results from auricular systole begins at a time distance of 0.20 sec. from the carotid pulse. In papers on the nodal rhythm by various writers there are several figures of venous, arterial, and apex tracings which are used to show that there is no wave in the venous pulse at the time when such a wave normally occurs, but that there is one at a later phase of the cardiac cycle, forming a combined wave with that attributed to ventricular systole. But if these tracings be carefully examined and measured with a pair of compasses and the standards of time agreed upon for identifying the various waves in the tracings, a wave will be found in many of these venous tracings which occurs at the proper time for an *a* wave and which could have been caused by auricular systole.

There is also very probably some increase in the interval which elapses between the onset of ventricular systole in cases of mitral incompetence and the carotid pulse. This is, as has been pointed out, due to delay in the development of sufficient intra-ventricular force to open the semilunar valves owing to blood escaping back into the left auricle. Such a delay has been shown on the tracings of Weiss and Joachim. These writers estimate the time of the normal interval to be 0.08 sec., and of the interval in mitral regurgitation, 0.12 to 0.15 sec., according to the condition of the left ventricle and the incompetent mitral valve.

Two examples of venous tracings in which it is stated that no wave due to auricular systole occurs, but in which I consider one is present, may be mentioned. Mackenzie's Fig. 185 (Fig. 12) is used to show a jugular pulse of the ventricular form with bifurcated wave due to synchronous action of auricular systole and ventricular systole, and 'not the slightest sign of the auricular wave *a* at its normal period in the cardiac cycle'. Here are six jugular pulse-beats, and in four, but especially in the first two of them, are distinct waves at the period of auricular systole. No presystolic murmur was heard at the time the tracing was taken.

In Hay's book, Fig. 85 (Fig. 13) is recorded to show that auricle and ventricle contract simultaneously, and that there is no *a* wave in the jugular pulse-beats; whereas by my measurements there is a distinct wave in most pulse-beats at the time of auricular systole, i. e. 0.20 sec. before the time of the carotid wave.

In concluding his consideration of the sequence of the contractions of the different parts of the heart, Gaskell writes: 'Considering, then, the diffi-

culty of deciding whether in any given case a contraction does or does not take place, we may sum up this section by saying that in all cases the sequence of the contraction of the different parts of the heart is most probably due to the passage of a wave of contraction along muscular tissue, even though under certain conditions this contraction may be so small as not to be visible by ordinary methods of observation.' McWilliam also mentions cases, according

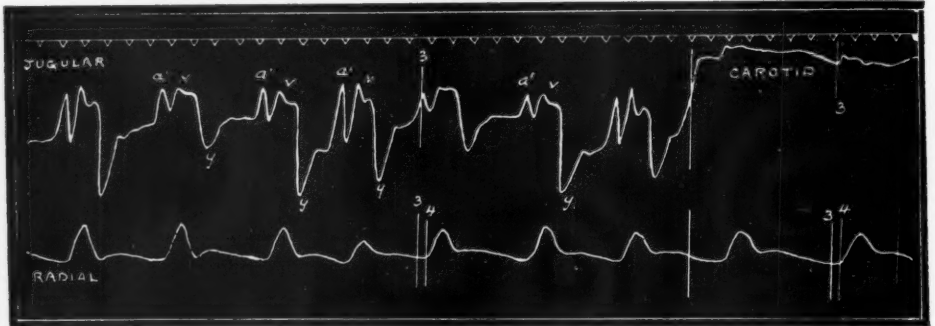


FIG. 12.

to Gaskell, where his curves showed complete cessation of auricular contractions, although upon close inspection he convinced himself that the auricles were still beating very feebly. Such being the case, it will be readily acknowledged that such auricular contractions could cause no wave in the jugular pulse. But whilst, on the other hand, Fredericq states that fibrillary contractions, though passing from one auricle to another over the bridge of connecting muscular tissue, cannot pass from the auricle to the ventricle, it is easily conceivable that

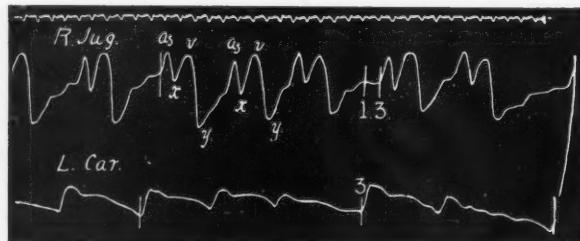


FIG. 13.

contractions of the auricle muscle may be sufficiently more marked than those of fibrillary nature to be able to excite contraction of the ventricle, and yet be too feeble to cause a wave in the jugular pulse.

2. The stated absence of an a wave in the apex-beat cardiograms is open to similar criticism (see Fig. 8).

3. Disappearance of the wave in the liver pulse due to auricular systole. Fig. 66 (Fig. 14) is offered by Mackenzie to show that in nodal rhythm there

is no wave in the liver pulse at the time of a normal α wave; but in every one of the liver pulse-beats a wave commences at the proper time for the α wave (i. e. 0.30 sec. before the time of the radial pulse). At the top of this wave another is added which is marked as being due to an auricular systole synchronous with that of the ventricle. A possible explanation of this type of phlebogram will be suggested on a later page.

This is the only figure of a liver pulse-tracing in which the time intervals are recorded, but in Figs. 61 and 192 there are also slight waves in some of the pulse-beats about the time of auricular systole, although it is stated in the legend of the figures that none occurs. It is difficult to be definite here as there is no time marked on either tracing.

4 and 5. Absence of presystolic murmurs due to the contraction of the left or much less commonly right auricle.

The rhythm of the crescendo murmur. I showed in the *British Medical Journal*, Aug. 28, 1909, that there is a considerable volume of evidence which



FIG. 14.

proves conclusively, in my opinion, that this murmur is early ventricular systolic or practically presphygmie in rhythm, but Mackenzie thinks that the proofs in favour of the auricular systolic rhythm are indisputable. I will, therefore, now consider the evidence on which he bases this opinion, as far as I can find such in his most recent work.

The presystolic murmur, also called the crescendo murmur, is 'of crescendo character, rising in pitch till it ends in the first sound'. Whilst in one place it is stated to be due to the contraction of the left auricle forcing blood through the narrowed mitral orifice (or right auricle and tricuspid orifice), on another page, in a paragraph on 'The Presystolic Murmur of Ventricular Origin', it is acknowledged that a slight regurgitation through the mitral orifice at the beginning of ventricular systole may produce the brief crescendo murmur'; this concession is made because Mackenzie has heard a brief crescendo murmur when the venous tracing showed that there was no auricular systole at the normal time. In spite of such an important concession Mackenzie thinks that this peculiar murmur, which he acknowledges is regurgitant sometimes, can also be

produced in the direct flow of blood through the heart, and that the evidences of auricular systole producing a presystolic murmur are indisputable.

IV. *What are the Arguments by which the Auricular Systolic Rhythm of the Crescendo Murmur is supported?*

The most important argument is that when a crescendo murmur occurs there is generally, *but not always*, a wave in the jugular pulse which is attributed to auricular systole, and which is not present when the crescendo murmur is no longer heard. In support of this contention some tracings are given in which the position of a crescendo murmur in the cardiac cycle is indicated by shading added by hand where the observer by his synchronous eye and ear observation thinks it ought to go.

Nearly all the cardio-vascular work of English observers is carried out with instruments which only record one-fifth of a second time intervals, whilst Wenckebach's tracings show one-thirtieth of a second, and Weiss and Joachim's and other Continental observers' one-hundredth second intervals, and murmurs timed with the ear are recorded by hand on tracings where the observer con-

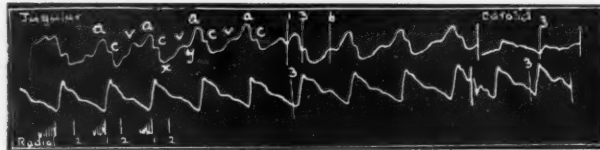


FIG. 15.

siders, from his synchronous ear and eye observation, they ought to go. From these tracings jugular pulse deductions are made.

The time-record of murmurs which may occupy less than 0.1 sec. (a crescendo murmur, if caused by auricular systole, cannot occupy more than 0.1 sec., as this is said to be constant), especially when the heart is beating quickly, say 90 or more per minute, is not very satisfactory for scientific purposes. How unsatisfactory such records are for scientific purposes can easily be seen by a careful inspection of them. In Mackenzie's Fig. 183 (Fig. 15) there is shown a crescendo murmur of equal length to the interval marked on the figure between the onset of auricular systole and the carotid pulse, i. e. 0.2 sec. in this instance. The murmur terminates just before a wave marked *c* in the jugular pulse which is meant to indicate the carotid pulse. This occurs normally about 0.08 sec. after the onset of ventricular systole, and after the first sound of the heart which always terminates a true crescendo murmur, and therefore at least 0.1 sec. (allowing for conduction) after the termination of the auricular systole which is actually causing the murmur. That is, the murmur is pictured at twice its proper length and twice as long as the duration of the producing force according to the modern teaching.

The prolongation of a presystolic murmur well beyond the termination of auricular systole is well shown in other figures. Thus in Fig. 272 (Fig. 16) a crescendo murmur of about 0.3 sec. duration by measurement with compasses is shown, and the first heart-sound is placed to end with the beginning of the radial pulse, which occurs normally 0.2 sec. after the onset of ventricular systole. If the first sound were placed accurately in relation to the jugular pulse-tracing

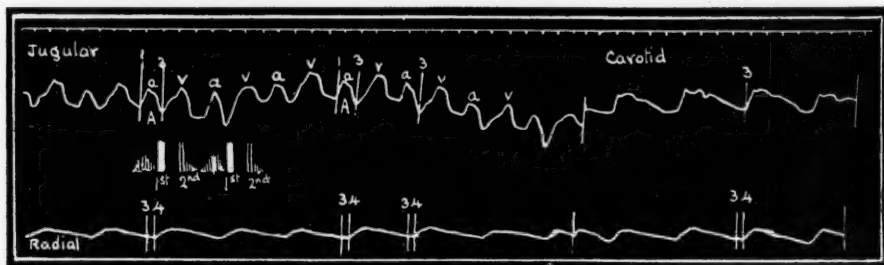


FIG. 16.

in this figure, that is, distinctly before the time of the carotid pulse marked on the radial tracing, it would appear to be synchronous with the apex of the wave marked *a* and attributed to auricular systole. It may be pointed out that if careful measurements be made with compasses the line drawn on the jugular tracing to indicate the time of the carotid pulse will be found to be about 0.05 of a sec. out of position as compared with the same line on the radial pulse. Also it will be seen, if any of the waves marked *a* be carefully studied

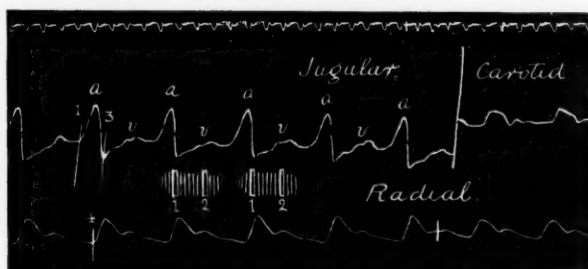


FIG. 17.

even with the naked eye, that they are composite waves, and have smaller waves on them which must be caused by additional factors to the auricular systole to which alone they are attributed.

Similar criticism can be made of tracing Fig. 265 in Mackenzie's Plate V, the first sound being placed sometimes well before, at other times after the time of the carotid pulse. In Fig. 123 of Hay's book (Fig. 17) is drawn a crescendo murmur which measures from its beginning to its termination with the first sound of the

heart 0.20 sec. The *a-c* interval as marked is about 0.35 sec. in duration. Of this time the duration of auricular systole is less than 0.1 sec. (constant), and the period between the onset of ventricular systole and the carotid pulse is also about 0.08 sec. (constant). Adding these two items together we get 0.18 sec., and subtracting this from 0.35 we have left a space of 0.17 sec. intervening between the end of auricular systole and the beginning of ventricular systole of cardiac muscle pause, and yet the crescendo murmur which is caused by auricular systole is being heard through this 0.17 sec. of auricular rest. The method, therefore, of marking murmurs by hand on pulse records is too inaccurate to be used for scientific proof of the time of any cardio-vascular phenomena.

But apart from the unsatisfactory character of these records with the murmur added by hand, the tracings are useful with only the statements as to the presence or absence of a crescendo murmur when they were taken. Let us take in the first place some tracings used to prove that when a crescendo murmur is present there is an *a* wave in the jugular pulse, and none when the murmur is absent. Mackenzie's Fig. 183 (Fig. 15) is from a case in which a crescendo murmur was heard, and is a tracing of a characteristic auricular venous pulse. Fig. 185 (Fig. 12) was taken when the crescendo murmur had disappeared and the venous pulse was of the ventricular form with no *a* wave preceding the time of the carotid pulse. On careful measurement, however, a more or less distinct wave at the proper time for the *a* wave in the normal jugular pulse will be easily seen in some of the jugular pulse-beats in this figure. The same observations apply to Figs. 233 and 234. In the latter the *a* wave is wrongly marked as I measure it, but a crescendo murmur was present. In Fig. 236, with no crescendo murmur, slight *a* waves are seen in two or three of the venous pulse-beats where none are supposed to exist.

Lewis's case referred to under the paragraphs on conductivity (Fig. 6) may be mentioned again here. In it, although the crescendo murmur disappeared, there was, as Lewis himself shows, a wave in the venous pulse due to auricular systole, and it was assumed therefore that whilst the right auricle must have been contracting to produce the *a* wave, the left auricle could not possibly have been contracting because there was no crescendo murmur. Hence activity of right auricle and paralysis of left auricle.

Important evidence as to the time of the occurrence of the crescendo murmur is afforded by the observations of Weiss and Joachim with their phonoscope. They show distinctly by their records the time-relations of the sounds and murmurs of the heart with tracings from the apex beat and from the carotid pulse. Their conclusions are:—

1. The distance from the onset of ventricular systole to the rise of the carotid pulse in a normal heart is 0.08 to 0.09 sec.
2. In mitral regurgitation this distance is increased from 0.125 to 0.15 sec., according to the degree of muscle failure present.

The crescendo murmur of mitral stenosis, which in my opinion is of

presphygmie or regurgitant rhythm, occurs within the time they allow for the prolongation of the presphygmie interval in regurgitation, namely, 0.15 sec.

To summarize this consideration of the theory that the crescendo murmur is indisputably caused by auricular systole:—

1. Mackenzie has heard crescendo murmurs in cases in which he saw no evidence of auricular systole at the normal time in the jugular pulse.

2. Lewis describes a case in which a crescendo murmur disappeared but still a wave was present in the jugular pulse which he considered to be due to right auricular systole.

3. The crescendo murmur when added by hand to a tracing is always drawn at more than double the duration of auricular systole, and extends over a period of time which under the constant duration of auricular systole theory covers a complete period of muscular inactivity on the part of the auricle.

The theory, then, that the crescendo murmur is caused by auricular systole is, on its supporters' own showing, not only highly disputable, but even altogether untenable, and it cannot be used in support of the theory that the contraction of the ventricle precedes that of the auricle, as is contended in the theory of the 'nodal rhythm' of the heart in mitral stenosis.

From such a consideration of the nodal rhythm theory of the action of the heart in certain forms of mitral disease it appears that there is no unquestionable evidence in its support.

The explanation offered of the ventricular, or nodal rhythm, type of phlebogram seems unnecessarily unphysiological when a careful consideration of the conditions present when such a pulse-tracing is recorded can offer a more probable and easier interpretation. Let us consider these conditions.

Interpretation of Venous Pulses, Normal and Abnormal.

In explaining the causation of the various waves and depressions in jugular pulse-tracings it has always appeared to me that observers do not pay sufficient attention to the effect which the anatomical relations of the aorta with the auricles and superior vena cava may have on the venous pulse, both in health and, especially, in disease. The relations which I refer to are (1) that the ascending aorta is in contact with both auricles, especially the left auricle, and with the superior vena cava in one or other part of its extent, and (2) that the pulmonary artery is in contact with the left auricle. These contacts, which occur normally, are much more marked when the auricles and the superior vena cava are dilated, as is so often the case in heart disease, especially in mitral and tricuspid valve lesions.

A dilated left auricle is not only in contact with the ascending aorta, but it actually pushes the vessel forward to a marked degree, as Keith shows

in Fig. 9 of his paper on 'The Jugular Pulse'. In the *normal* state of distension of the veins with normal filling and emptying of the auricles the contacts with the aorta will be most marked at the end of ventricular systole, that is, when the venous system is most distended; but in *abnormal* conditions when the auricles and veins are over-full from diseased conditions the contacts, whilst still being greatest at the same period of the normal cardiac cycle, are permanently abnormally marked. Such being the case it seems wellnigh impossible for pulsations in these large arteries not to be communicated to the blood in the distended auricles and the superior vena cava and be transmitted through what may be called a venous tambour system to be recorded in the pulsations of the jugular vein. Aortic and pulmonary artery pulsations ought also to be transmitted to the liver.

The c wave. This small wave which follows the *a* wave in a normal jugular pulse is considered by most observers to be communicated from the carotid or subclavian artery to the jugular bulb. But whilst there are substantial reasons for this view, it is possible that the wave is caused by distension of the aorta communicating an impulse to the superior vena cava which is transmitted as an impulse wave through the vein to the jugular bulb. The superior vena cava at the time of the opening of the aortic valve is well distended, its emptying, which is due to auricular dilatation, not having had time to progress far. If the *c* wave be due to an aortic impulse it will be more marked and more prolonged when there is an abnormal venous distension and one which is due to dilatation of the auricle and imperfect contraction of this chamber, especially in obstructive lesion of the tricuspid valve.

The final small wave in the phlebogram which arises at the closure of the semilunar valves is likewise possibly due to the dicrotic or rebound wave of the aortic pulse being transmitted through the superior vena cava, then at its maximum distension, to the jugular pulse. This wave again will be most marked with abnormally distended veins. This final wave is figured by Hay to occur in all the varieties of the auricular and ventricular forms of venous pulses. It is curious that this wave is constant in all these venous pulses whether auricular or ventricular in type, and the distension of the veins, the contact with the aorta, and the movements of the blood in the aorta are always present, though in varying degrees.

That impulses from a contracting left auricle can be transmitted to the aortic column of blood and be recorded even on the radial pulse is acknowledged by Mackenzie when he suggests that in certain cases of heart-block small waves in the radial pulse may be caused by contractions of the left auricle (Fig. 119, 122, and 123).

Phlebo-cardiograms. There is the further and very important possibility, or even probability, that pathologically dilated auricles and distended venae cavae would be able to transmit movements of the ventricles of the heart and enable such to be recorded on the venous, especially the jugular, pulse.

Keith says that in every one of the hearts sent to him by Mackenzie and

from which the latter had obtained the nodal type of jugular pulse—that is, a pulse in which the jugular bulb was expanding or filling instead of emptying during ventricular systole—there was great dilatation of the auricle with a certain degree, sometimes more, sometimes less, of compression of the ventricle. In these hearts the auriculo-ventricular groove occupied the position corresponding to that of ventricular systole in the normal heart. In all cases where this type of jugular pulse occurs there is great distension of the venous cistern and of the auricle; the auricular base of the heart is pushed forwards so far in diastole, that during ventricular systole it cannot move forwards more, and

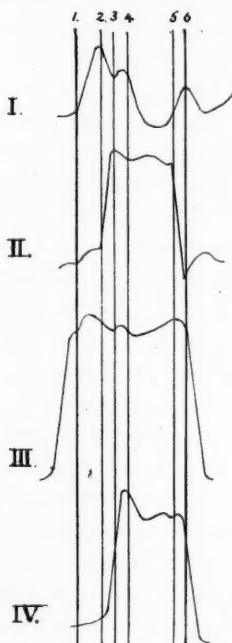


FIG. 18. 1, onset of *a-s*; 2, onset of *v-s*; 3, carotid pulse; 4, radial pulse; 5, closure of semilunar valves; 6, opening of *a-v* valves. I, Normal phlebogram; II, Cardiogram; III, Variety of auricular phlebogram; IV, Nodal rhythm phlebogram.

therefore there can be no expansion or dilatation of the auricle and no emptying of the jugular bulb during ventricular systole. There is a *permanent distension of the auricle under high venous pressure in these cases.*

It seems a fair conclusion to these anatomical statements, that if the ventricles of the heart are pushed forwards by the distended auricles which have a distended venous cistern behind them any movements of the auricles and ventricles must be transmitted by what may be called a venous tambour and be recorded by the venous, and especially by the jugular, pulse. If the jugular pulse-tracings which Keith refers to above, and shown by Wenckebach (Keith's Fig. 4, No. 6) and Hay, Fig. 77 v, be examined they will be found to be practically identical in form with the cardiogram records from the apex

beat, but its record begins at a later period of the cardiac cycle than does that of the apex cardiogram. Hay's Fig. 28 v is also of this nature, but with modifications. In the accompanying figure (Fig. 18) I have reproduced these tracings. There is probably more than a curious coincidence in the fact that the tracings from a nodal rhythm pulse and the apex cardiogram are so similar. At this point it will be advisable to point out the conditions which affect the production of a jugular pulse in cases of a dilated right auricle.

The exact nature of a phlebo-cardiogram recorded in the way I suggest must vary according to (1) the amount of distension of the venous cistern and the auricles, (2) the extent of the power of the auricles to contract, (3) the condition of the auriculo-ventricular orifice, i. e. whether this permits or obstructs the free flow of blood into the ventricle during diastole of this organ, and (4) the size of the ventricles.

We must bear in mind here the fact that the amount of blood in the superior vena cava and the auricles, and therefore the distension of these organs, is at its minimum during auricular diastole when the auricle retains its power of contracting, and therefore of dilating, and during ventricular diastole when the auricle is inert and over-distended.

The explanation of the nodal type of venous pulse which is generally offered is that there is no auricular systole at its proper time, but that this occurs after the onset of ventricular systole and results in a marked wave which arises after the end of the presphygmie interval and synchronously with the normal carotid wave. It is said that ventricular systole precedes auricular systole by 0.1 sec., and that the stimulus for both these contractions arises not at the sino-auricular but at the α -v node.

Such an explanation of the ventricular form of venous pulse is unsatisfactory, for this form of pulse often occurs paroxysmally in a heart which at other times beats in the ordinary way, that is, with the auricle contracting before the ventricle to a stimulus arising at the sino-auricular node. Thus it will be seen that there can be no permanent disease of the sino-auricular node, otherwise the normal rhythm of auricle-before-ventricle heart-beat could not occur at all and the ventricle-before-auricle beat must be permanent.

Keith states that there is no mechanism in the mammalian heart which can completely prevent regurgitation of the blood from the right auricle if that chamber be distended, and he concludes that the expansion of the jugular bulb during auricular systole in cases where the right auricle is distended is directly due to the contraction of the auricle, but in a condition of health it is probably due to the arrest of the venous outflow. This means that in cases of distension of the right auricle, when the auricle is able to contract, blood regurgitates into the superior vena cava. This will mean an impulse wave which will add to the wave of stagnation produced by the prevention of the flow of blood from the veins into the auricle, to be recorded at a later time than the stagnation wave, because a true pulse wave takes some time for its transmission in the vein against the direction of the flow of blood. This seems to me to be an

important fact not taken into consideration in explaining the normal and abnormal venous pulse-tracings, and which should be reckoned with.

The difficulty of excluding the occurrence of slight contractions of the auricle has already been pointed out.

Post-mortem Appearances in Nodal Rhythm.

Mackenzie writes concerning the post-mortem appearance of the hearts in which the 'nodal' rhythm occurred: 'For some years I have sent to Prof. Keith hearts affected with many forms of disease. . . . On comparing his descriptions with the clinical notes, I found, with one exception, that all the cases that had the nodal rhythm during life presented some evidence of change in the primitive cardiac tissue or in the artery supplying it. There were also found such changes in the auricular wall in a few cases as to suggest an interruption of the means of communication between the sino-auricular and the auriculo-ventricular nodes.'

Keith writes: 'In such hearts I have been unable to detect any positive microscopic lesion in either the sino-auricular or auriculo-ventricular node. The one feature present always is great dilatation of the auricle; hypertrophy of the taenia terminalis and muscoli pectinati. It is possible that, in such cases, the venous pressure within the auricle has become so great that conduction and contraction of the auricular musculature is so depressed that for all practical purposes the auricle is paralysed, as Mackenzie originally supposed.'

There is evidently, then, no definite lesion of the sino-auricular node, or of the *a-v* node, to cause the supposed varying origin of the seat of stimulus development. It may be contended, however, that there is temporary disturbance of the blood-supply of the sino-auricular node, such as is met with in angina pectoris or the local spasm of the blood-vessels of the foot in intermittent limp, but such a contention is not convincing.

In conclusion I submit that, apart from the failure of the evidence on which the nodal rhythm theory is supported which has been discussed previously, the explanation of the ventricular form of venous pulse which I offer, namely, that it is a phlebo-cardiogram, is quite probable and more in keeping with the normal physiology of the heart than that which depends on supposed alterations in the seat of stimulus production and consequent perversions of the relative rhythm of the auricle and ventricle.

Electro-cardiogram records, which are being taken and studied more and more widely daily, though they require great skill and apparatus too complicated for the ordinary clinician, will help to settle many disputed points in cardiology, especially when taken synchronously with tracings from Weiss and Joachim's phonoscope and the phlebograph. A few of such records have already been published. Thomas Lewis is carrying out most valuable work in England with the electro-cardiogram, and since this review was sent to press has published a very fine and convincing paper (*Heart*, Vol. I, No. 4), in which,

amongst other points, he shows that fibrillation of the auricle is very common in heart affections, and leads to absolute irregularity of the ventricle and the 'nodal' form of venous pulse. This fibrillation showers impulses rapidly and irregularly on the ventricle and may be accompanied by all grades of heart-block. He finds that a rhythm does start in the neighbourhood of the node of Tawara, but it is a rare affection and is distinct from the mechanism which produces complete irregularity.

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THE MOTOR FUNCTIONS OF THE STOMACH

BY ARTHUR F. HERTZ

PART I.—PHYSIOLOGY

THE foundation of our knowledge of the movements of the stomach was laid in 1679 by Wepfer, who observed peristalsis in the exposed organ of living wolves, dogs, and cats. Except for some similar experiments performed by Schwartz and Haller in the eighteenth century, no further advance was made until 1833, when Beaumont, a surgeon in the United States army, published his researches on the stomach of Alexis St. Martin, who, as the result of an accidental gunshot wound, had a gastric fistula.

In more recent years the experiments of Wepfer have been frequently repeated, and the movements of the excised stomach, placed in a moist chamber kept at the body temperature, have been investigated. Then Pawlow and his pupils, with the aid of oesophageal, gastric, and duodenal fistulae, made a number of important observations on the motor activity of the stomach and pylorus in the course of their investigations on the work of the digestive glands.

No observations on gastric movements under really physiological conditions had ever been made, when Cannon (1898) and Roux and Balthazar independently made observations on the stomachs of animals by means of the X-rays.¹ This method was first employed on man by Roux and Balthazar, but no very definite results were obtained until several years later, after Rieder had shown that large doses of bismuth salts could be taken without danger. A further improvement in technique was effected by the substitution of the oxychloride for other salts of bismuth, the oxychloride being the only one which is chemically inert in the stomach, and which consequently does not interfere with the important mechanism by which the hydrochloric acid of the gastric juice controls the activity of the pylorus. In my own observations I have most frequently given two ounces of the salt in bread and milk or porridge, but for special investigations other methods of administration are of course required.

The use of the X-rays has demonstrated that the normal position and shape of the stomach is so different from what was formerly described that it will be

¹ Cannon's first communication on the subject was in May, 1897, Roux and Balthazar's in June, 1897.

[Q.J.M., July, 1910.]

well to consider its anatomy before describing its movements. The nomenclature adopted is that recommended by Cunningham: it is mainly due to His and Jonnesco, and its adoption by physiologists, pathologists, and clinicians would add greatly to the value of their publications.

The *fundus* is defined as the part of the stomach which lies above a horizontal plane passing through the cardiac orifice (His). It is nearly hemispherical in shape and lies in the concavity of the left half of the diaphragm. All who have used the X-rays for examining the stomach agree that in the vertical position the *body* is of nearly uniform width and is situated entirely to the left of the middle line (Fig. 1). It is either vertical or, especially in

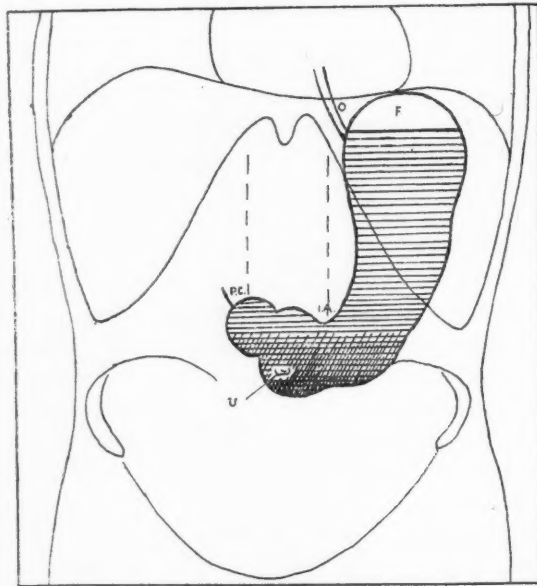


FIG. 1. Normal stomach in vertical position.

O=end of oesophagus; F=fundus of stomach, containing gas; I.A.=incisura angularis; P.C.=pyloric canal; U=umbilicus.

men, slightly inclined towards the right. Its separation from the *pyloric part* of the stomach is indefinite, but it can be recognized in frozen or formalin-fixed specimens, and with the X-rays in the vertical position, by the *incisura angularis* (His) on the lesser curvature and by a less constant depression on the greater curvature (*vide infra*). The pyloric part of the stomach consists of the *pyloric vestibule* and *pyloric canal*.² The pyloric vestibule is directed upwards as it turns towards the right and at the same time slightly backwards. It always extends to the right of the middle line, and not infrequently as far

² The term *pyloric antrum* has been used with so many different meanings that it seems best to discard it entirely, as recommended by Cunningham.

as the left lateral plane of Addison (half-way between the anterior superior spine of the ilium and the median plane).

The work of Jonnesco, Erik Müller, and Cunningham on the anatomy of the pylorus is of great importance for the proper understanding of its functions. They have shown that there is a definite tubular part of the pyloric end of the stomach, about 3 cm. in length, which has been called by Jonnesco the pyloric canal. It makes a sharp angle with the pyloric vestibule, as it passes backwards and slightly upwards and to the right in contact with the quadrate lobe of the liver. It is relatively long in infants, and in them its separation from the pyloric vestibule is sharper than in adults. Its termination projects into the duodenum, producing, as Cunningham has pointed out, a very striking resemblance to the portio vaginalis of the cervix uteri (Fig. 2). Both the circular

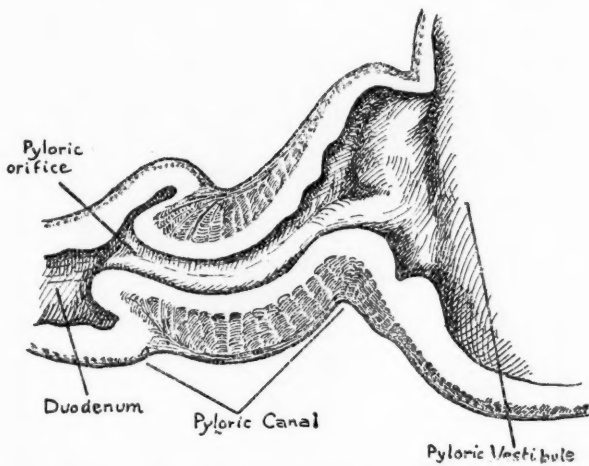


FIG. 2. Section through the pyloric part of the stomach of a child aged 2 years. Magnified two diameters. (After Cunningham.)

and longitudinal muscular coats are much thicker in the canal than in any other part of the stomach. The circular fibres are disposed in the form of a sphincter, which attains its greatest development at the duodeno-pyloric junction, where it is separated by a distinct connective-tissue septum from the circular coat of the duodenum. Only a few of the more superficial longitudinal fibres are continuous with those of the duodenum, the majority forming distinct fasciculi, which penetrate the substance of the sphincter, in which some end, whilst others reach the subjacent submucous tissue.

In our observations on seventeen healthy young men, Dr. C. J. Morton and I found that in the vertical position the greater curvature was invariably below the umbilicus, the distance below the umbilicus varying between 1 and 12 cm. with an average of $5\frac{1}{2}$ cm. In 36 men and 54 women of several ages, many of whom were suffering from various diseases, but none from any gastric

disorder, Groedel found that the average distance of the lowest point of the greater curvature below the umbilicus was $2\frac{1}{2}$ cm. and 5 cm. respectively for the two sexes. Holz knecht and Pfahler, however, regard as normal only that form of stomach which, according to their ideas, is the best capable of performing its functions satisfactorily. In their 'normal' stomach, which they admit is very rarely seen even in apparently healthy people, the pylorus is the lowest point and the greater curvature does not reach the umbilicus. I have only observed this four times, in each case in patients who had been very carefully dieted for a long period on account of gastric symptoms due to various causes (Fig. 3). I agree with Rieder, B  cl  re, and Groedel, that it would be most unreasonable to regard a form of stomach, which is so rarely

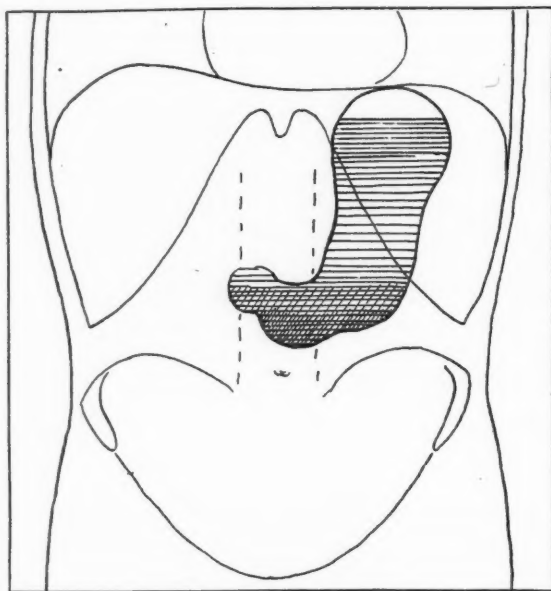


FIG. 3. Contracted form of stomach in vertical position from a patient who had been strictly dieted and resting in bed for a month.

met with, as the only normal condition. In the large majority of healthy individuals, who take an ordinary quantity of food, the greater curvature reaches below the umbilicus; the form in which the pylorus is the lowest point of the stomach appears to occur only in individuals, who, in spite of possessing a normal stomach, habitually take very small meals.

In the horizontal position Morton and I found that the lowest point of the greater curvature is from 2 to 10 cm. higher than in the vertical position. Consequently in most individuals it is slightly above the umbilicus (Fig. 4). The diaphragm also rises slightly when the recumbent position is assumed,

and the highest part of the fundus rises with it. The position of the pylorus remains almost unaltered.

The condition of the abdominal muscles has a great influence on the position of the stomach. Morton and I found that in normal people the body of the stomach can be lifted from 5 to 13 cm. by a voluntary contraction of the abdominal muscles, and can be caused to drop down by their voluntary relaxation. Similar observations have been recorded by Pfahler.

The vertical position of the stomach was also observed by Pfahler in children aged respectively 10 years, 3 years, and 7 months, and by Groedel in one child of 3 and in sixteen between 12 and 16. But, according to the X-ray observations of Leven and Barret, in young infants the stomach is

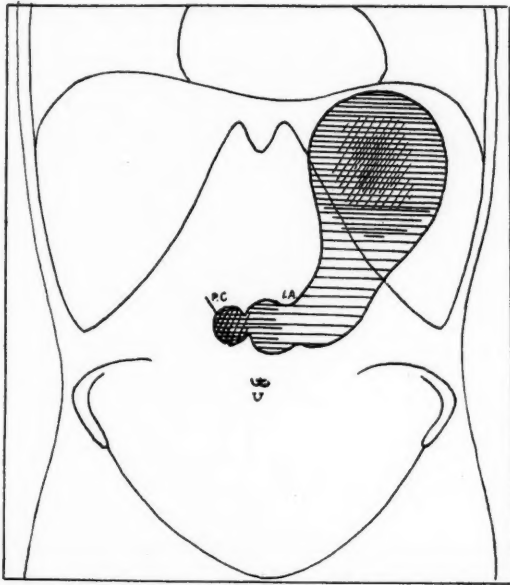


FIG. 4. Normal stomach in horizontal position.

normally horizontal in whatever position they are examined; it extends well to the right of the middle line under cover of the liver.

The stomach always contains gas, the amount varying considerably in different individuals; in the vertical position it is all collected in the fundus, where it can be seen with the X-rays as a translucent area under the diaphragm. After a meal containing bismuth the horizontal upper limit of the gastric contents can be clearly seen, the upper part of the fundus being still filled with gas (Figs. 1, 3, and 6). On shaking the body the splashing of the fluid or semi-fluid gastric contents can be watched, and on leaning to one side the horizontal upper limit can be seen to be maintained. Rhythmical waves, due to the impact of the heart, are frequently visible.

X-ray observations have shown that in the empty condition only the pear-shaped upper third of the stomach contains gas, the rest of the organ passing to the pylorus in the form of a collapsed tube, which corresponds in position to the lesser curvature of the filled stomach (Fig. 5). Its muscular coat is in slight tonic contraction and the mucous membrane is thrown into folds.

When food enters the stomach through the cardiac orifice of an individual who is sitting or standing, it runs down the mucous membrane to the point where the gastric walls are in contact with each other. When a small quantity of food has been swallowed, its weight is sufficient to overcome the resistance produced at the entrance to the body of the stomach, after which it rapidly passes down to reach the pyloric part. The more fluid the food the more

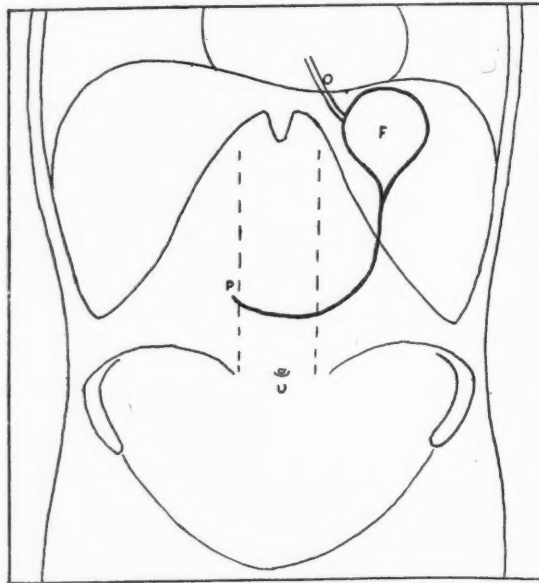


FIG. 5. Empty stomach in vertical position.

o = oesophagus; F = gas-containing upper third of stomach; P = pylorus; u = umbilicus.

rapidly does this occur. Braeuning has suggested that the resistance offered to the passage of food into the body of the stomach is the result of a reflex from the oesophagus, which is called forth more readily by solids than fluids and which gives rise to an increase in the muscular tone of the stomach.

It was formerly believed that the stomach was a thin-walled flaccid sac. Luschka, in 1873, was the first to insist that the healthy stomach, by contraction of its muscular coat, adapts itself to its contents and that its walls are firm and thick when it is empty. By introducing a tube connected with a manometer into the stomach of normal individuals, Moritz (1895), and more recently Sick and Keith, have shown that the minimum intragastric pressure

remains steadily between 4 and 6 mm. of mercury, whether the organ is full or almost empty. Leven and Barret have also demonstrated this adaptation of the tone of the stomach to the volume of its contents by means of X-ray examinations in the erect position: in normal adults there is very little difference in the position of the upper limit of the semi-fluid gastric contents, whether their volume be 40 or 400 cm. I have been able to confirm these observations on numerous occasions, the upper limit of the gastric contents remaining almost constant so long as their volume exceeds about an ounce and a half (Fig. 6). Moreover, the greater curvature is very little depressed as the stomach is gradually filled.

The nature of the mechanism by means of which the stomach adapts itself to the volume of its contents in such a way that the internal pressure remains constant is more complicated than might at first be supposed. Grützner (1904)

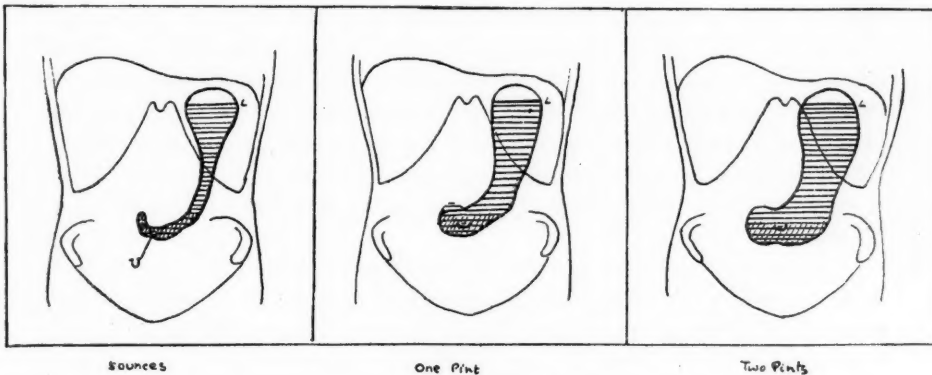


FIG. 6. Gradual filling of stomach.

U = umbilicus; L = upper limit of gastric contents.

pointed out that a mere relaxation of the tonic contraction of the fibres of the muscular coats of the stomach would be quite insufficient to account for the enormous variations which may occur in the volume of the stomach without any accompanying change in the internal pressure. He suggested that a rearrangement of the muscle-fibres must simultaneously occur. Albert Müller has proved that this supposition is correct by comparing the histological appearances of the stomachs of frogs when empty and when filled. He found that the length of the muscle-fibres in the filled stomach was only one and a half to three times that of the fibres in the empty and contracted stomach, although the circumference of the former was five times that of the latter. The increased length of the relaxed fibres was therefore insufficient to account for the increased volume of the organ. A rearrangement of the fibres was found to be a more important factor, as in the contracted stomach of the frog they are arranged in from fifteen to twenty layers, whereas in the full stomach the muscular coat consists of only two or three layers of fibres. Müller and

Saxl (1908) suggest that the adaptation of the stomach to the volume of its contents results from a reflex which originates in the oesophagus during swallowing and is conveyed to the stomach by the vagus, but the mechanism which gives rise to the rearrangement of the individual muscle-fibres is at present quite unexplained.

Kelling has shown that another reflex mechanism exists, by means of which the tone of the muscles of the abdominal wall adapts itself to the varying volume of the contents of the alimentary canal. In the absence of such a reflex the taking of a meal of moderate size would result in a rise in intra-abdominal pressure, which would be very considerable in animals, as, according to Kelling's measurement, the volume of the abdominal contents of a dog may be increased as much as 100 per cent. after a meal. If air or fluid is injected into the peritoneal cavity, the intra-abdominal pressure at once increases, as the reflex adaptation of the tone of the abdominal muscles only occurs with alterations in the volume of the contents of the hollow abdominal viscera.

Schwarz and Kreuzfuchs have shown that towards the end of gastric digestion the lower border of the stomach rises about 4 cm., and its tone only slowly diminishes after it is completely empty. Hence if a meal is taken almost immediately after the stomach has become empty, the greater curvature falls 4 or 5 cm. when the stomach becomes moderately filled, whereas if the stomach has been long empty the lowest point does not drop more than $1\frac{1}{2}$ cm.

The tone of the stomach is not fully developed in infants, as the first food which enters the stomach reaches the pyloric part at once; as the volume of the contents increases, the upper limit steadily rises and the volume of air in the fundus gets smaller. Thus the total size of the gastric cavity increases only slightly as the amount of its contents increases. But a few minutes after a feed of 80 cm. or more the stomach of an infant suddenly contracts to a more globular form, which it maintains until the organ is emptied (Leven and Barret).

When an ordinary meal is taken by an individual lying on his back or his left side, it reaches the pylorus much more slowly than in the vertical position (Censé and Delaforge). If only a small quantity is taken at a time, it causes the fundus to bulge, but does not even touch the entrance to the collapsed part of the stomach (Holzknecht). Hence the very small feeds often given to bedridden patients remain in the fundus unless the erect or semi-recumbent position is assumed. Only when two or three such feeds have been taken will sufficient material be present to reach the entrance into the body of the stomach. If a patient is unable to sit up, it is therefore better to give meals of moderate size at intervals of a few hours instead of frequent very small feeds.

No peristalsis occurs in the fundus and upper part of the body of the stomach, the muscular coat of which is much thinner than that of the pyloric part. The upper half of the stomach acts as a storehouse for the food; by steady diminution in its volume, due to a constant increase in the tonic contraction of its musculature, it doles out food to the active pyloric half in such a way that

after the conclusion of the meal the contents of the latter diminish much less rapidly in volume than those of the former.

As soon as food enters the pyloric part of the stomach peristalsis begins; under normal conditions in the vertical position this occurs within a minute or two of the commencement of the meal. Each peristaltic wave starts as a constriction near the middle of the body of the stomach. The constriction is much more marked on the greater than on the lesser curvature, and it deepens as it slowly progresses towards the pylorus. About one inch from the entrance to the pyloric canal it reaches such a depth that part of the pyloric vestibule becomes almost completely separated from the rest of the stomach, and in some cases separation is finally complete. The part thus cut off then diminishes in size in every direction, owing, perhaps, to the contraction of longitudinal muscle

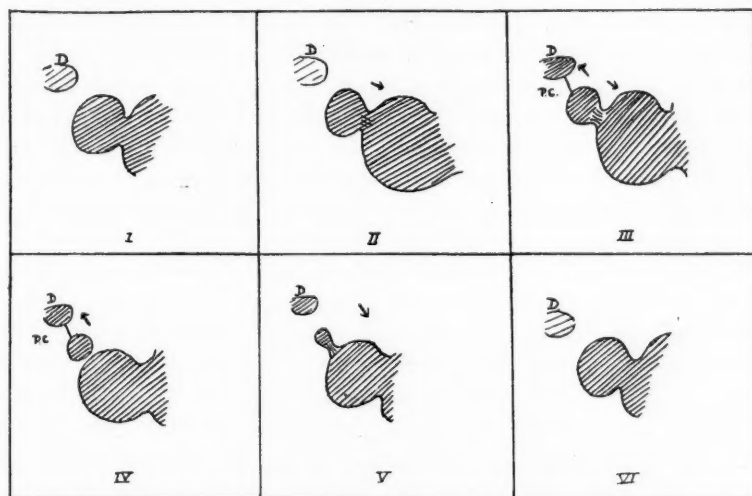


FIG. 7. Pyloric peristalsis. P.C. = pyloric canal; D = duodenum.

The arrows indicate the direction in which the food is moving—forward into the duodenum through the pyloric canal, or backwards into the pyloric vestibule.

fibres in addition to the further progress of the peristaltic wave. As a result some of its contents are from the first forced through the pyloric canal, the remainder being forced back as an axial reflux stream into the stomach.

As a result of the study of a number of series of instantaneous skiagrams, Kästle, Rieder, and Rosenthal conclude that the separation of the extreme pyloric end from the rest of the stomach is never complete. I have, however, several times seen a complete separation, but only after a considerable reflux into the stomach had already taken place (Fig. 7). In some cases the very small quantity of chyme present in the completely separated part of the stomach is all forced through the pyloric canal into the duodenum: in other cases the resistance offered by the pyloric sphincter is too great, so that finally the separation again becomes incomplete and some of the chyme is forced back into the stomach

by the further progress of the peristaltic wave, which only stops when it reaches the pyloric sphincter (Fig. 7, V). The peristalsis breaks up the food and mixes it thoroughly with the gastric juice. The contents of the pyloric part of the stomach are consequently more fluid and more homogeneous than those of the upper part.

The waves occur at regular intervals of 15 to 20 seconds, and three or four are present simultaneously. They increase in strength as digestion proceeds, and continue without intermission until the stomach is empty—between one and four hours after the meal, depending on its bulk and composition.

The rhythm can occasionally be distinguished by auscultation as well as by means of the X-rays. Cannon (1905), listening over his own pylorus, heard loud, rattling, explosive sounds, which occurred regularly every 20 seconds. They were most obvious after food of a spongy nature had been taken, and when he lay down on his back or left side. Though we have repeatedly tried to confirm this observation, we have rarely succeeded. On one occasion we heard sounds answering to Cannon's description, which recurred five times at intervals of 20 seconds; in another individual we once heard similar sounds recur four times at intervals of 18 seconds. We have also twice listened to the abdomen of individuals who had taken a special frothy meal, as recommended for the purpose by Cannon. In the case of one of them we heard a series of sharp pops repeated with perfect regularity every 17 seconds for about five minutes; in the other we could distinguish no rhythmical sounds.

The relative importance of the various stimuli which cause gastric peristalsis is not clearly known, but it is probable that mechanical stimulants are more important than chemical. Thus peristalsis does not vary greatly according to the nature of the food so long as the quantity and consistence are unaltered. The stretching of the muscular coat of the stomach by the mere entry of food into the stomach is probably the chief stimulus to its activity (Ducceschi). The mere contact of smooth objects with the gastric mucous membrane has no effect, but irregularly shaped objects, especially if they are hard, undoubtedly stimulate gastric peristalsis. Beaumont found that the introduction of a large thermometer through the gastric fistula of Alexis St. Martin at once gave rise to powerful contractions. The activity of peristalsis thus varies with the consistence of the food which reaches the stomach, and this depends partly on the quantity of cellulose and other indigestible material present in it, partly on the amount of softening which has taken place in cooking, and partly on the extent to which further subdivision and softening of the food have resulted from chewing.

Abdominal massage can be seen with the X-rays to increase the strength of peristalsis. This corresponds with the well-known clinical fact that visible peristalsis can often be excited by massage in cases of pyloric obstruction.

Very contradictory results have been obtained by different observers as to the effect of the temperature of the food on the gastric movements. This is due to the difficulty in distinguishing between the results of changes in the activity of peristalsis and the results of the changes in the tone and the frequency

of relaxation of the pylorus. This increased rapidity in the discharge of the chyme from the stomach may be due to increased activity of peristalsis or diminished resistance offered by the pyloric sphincter. But the same factor may simultaneously stimulate peristalsis and increase the tone of the sphincter, so that increased peristalsis does not necessarily result in a rapid evacuation of the stomach. Physiological experiments have proved that heat and cold stimulate involuntary muscle-fibres to contract, and there is no doubt that cold, at any rate, directly stimulates contraction of the intestine. It is therefore highly probable that gastric peristalsis is stimulated by food which is hotter or colder than the body. The effect cannot, however, be great, as Hedblom and Cannon, working with the X-rays, did not observe any difference in the activity of peristalsis in cats whether the food was frozen or warmed to the body temperature or 60° C.

C. R. Metcalf, working in Cannon's laboratory, found that hot and cold applications to the skin of the abdomen had no influence on the gastric movements.

As a result of his investigations carried out in Pawlow's laboratory, Edelmänn concluded that hydrochloric acid is the chief chemical stimulant of peristalsis, the activity of which is proportional to the amount of acid present. These conclusions were confirmed by Hedblom and Cannon, who observed with the X-rays an increase in the depth and rapidity of the peristaltic waves when hydrochloric acid was added to the food. Edelmänn believes that the stimulating action of other chemical substances depends upon their power of calling forth a secretion of gastric juice. The stimulating action of the extractives of meat on gastric peristalsis corresponds with their stimulating action on gastric secretion, and the failure of peptone to increase peristalsis corresponds with its failure to excite secretion. Carbon dioxide (Penzoldt, Schüle) and alcohol (Gluziński, Klemperer) are also said to stimulate both secretion and peristalsis.

On account of the great importance of hydrochloric acid as a stimulant of gastric peristalsis bismuth oxychloride should always be used for X-ray investigations of the stomach instead of the carbonate, as a large dose of the latter neutralizes every trace of acid in the stomach. According to Edelmänn, peristalsis stops when the gastric contents are neutralized. This is certainly not the case in man, as peristalsis can be observed with the X-rays when bismuth carbonate is used, although I am convinced that it is less active than with the inert oxychloride.

There is no experimental evidence that strychnine has any effect on the gastric movements, but, according to A. Müller and Saxl (1909), it increases the tone to a considerable extent. Pilocarpine, physostigmine, quinine, nicotine, ergot, and caffeine were all found by Battelli to stimulate gastric peristalsis in animals, but Leclerc found that pilocarpine greatly delayed the evacuation of his own stomach. The inhibiting effect of atropine and chloral described by Battelli has also been recently denied, but Müller and Saxl found that they greatly increased the capacity of the stomach by diminishing its tone.

Cannon has shown that fat produces slower and weaker peristalsis than carbohydrate or protein. As it also inhibits the flow of gastric juice, and as it is the most concentrated food in existence, it can safely be given to patients with gastric or duodenal ulcer, when it is desired to give nourishment without causing gastric activity.

By examining sections of the frozen stomach of animals after they had been given foods of different kinds, Grützner (1905) discovered that when new food enters the partially filled stomach, it passes into the centre of the mass present in the fundus and displaces what is already there outwards. He also tested the reaction of the layers of the food and found that, at a time when the contents of the pyloric half were uniformly acid, only the outer layer of the contents of the fundus was acid and so probably the seat of gastric digestion, the central part being alkaline and therefore still undergoing salivary digestion. The important fact that salivary digestion can continue for a considerable time in the stomach was also proved by Cannon and Day, who found that after a meal of starch had been given to a cat, an equal percentage of sugar was present in the cardiac and pyloric divisions of the stomach after half an hour, but 80 per cent. more was present in unit volume in the cardiac half than in the pyloric half at the end of an hour, thus showing that the food in the middle of the fundus remained unmixed with the acid gastric juice, which had stopped the action of the ptyalin of the saliva in the pyloric end.

These results cannot, however, be directly applied to man, as, owing to his erect posture and the presence of air in the fundus, the contents of the oesophagus are discharged either on to or slightly below the upper surface of the gastric contents and not into the centre of the food, which in animals completely fills the fundus.

Sick has attempted to ascertain how far Grützner's results can be applied to man by removing the contents of the cardiac end of the stomach, and on other occasions those of the pyloric end, at different periods after a test meal of semi-fluid consistency had been given. A cachet containing carmine or charcoal was swallowed immediately after the test meal. Until fifteen or twenty minutes later the carmine and charcoal were only present in the cardiac half of the stomach, but in thirty or forty minutes they were present in all parts. The initial delay in their distribution is probably due partly to the time required for the solution of the cachet, and partly to the fact that, taken at the end of the meal, they would at first float on the surface of the gastric contents, with which they could only become gradually incorporated.

Finally Sick found that hydrochloric acid could be recognized in the fundus ten to fifteen minutes after the meal, but not until five to ten minutes later in the pyloric end: the total hydrochloric acid and the free hydrochloric acid steadily increased up to a maximum and then gradually declined in all parts of the stomach, but the quantity was always greater in the upper than in the lower part. Sick explains these differences as due to the fact that the glands of the fundus secrete pepsin and hydrochloric acid, whilst those of

the pyloric end of the stomach secrete pepsin and very little hydrochloric acid. This explanation receives support from histological and experimental observations on animals. Sick further concludes that the upper and lower parts of the stomach are functionally quite distinct.

On comparing these results with those of Cannon we find a remarkable contradiction: both Cannon and Sick think that the two parts of the stomach are functionally distinct, but, according to Cannon, the fundus of the cat, with its alkaline reaction, is the seat of salivary digestion, whilst, according to Sick, the fundus of man, with its acid reaction, is the seat of more active gastric digestion than the pyloric end of the stomach.

These contradictory results can best be explained by a consideration of the movements of the stomach. The first observations on the human stomach with the X-rays were made in the horizontal position. They showed that the movements corresponded closely to those observed by Cannon in the cat, and it was at first thought that they proved that the stomach was permanently divided into two parts, anatomically and functionally distinct, in one of which salivary and in the other gastric digestion occurred. Thus Gray described a definite 'sphincter aditus vestibuli'. But the apparent complete division into two parts was due to the bismuth falling into the most dependent parts of the organ—the fundus and the pyloric vestibule. This can readily be understood by examining an antero-posterior section of the body made to the left of the spine, when the relatively deep position of the fundus is seen.

My recent investigations have been made in the vertical as well as in the horizontal position, and the bismuth has been given with porridge, which suspends it much more satisfactorily than milk or the other preparations in common use. Numerous observations have demonstrated that there is no real division of the stomach into two parts. The peristaltic contraction begins near the centre of the stomach, where it produces a shallow depression, which is not infrequently visible *post mortem*, if the viscera are preserved by modern methods³ (Cunningham). The contraction, however, is not fixed, but moves along as a wave, and it produces nothing approaching a complete division of the stomach into two parts until it reaches the pyloric vestibule. Even there the division, though it is generally complete, is constantly moving towards the pylorus and is absent in the intervals between the arrival of the peristaltic waves.

As there is no anatomical division between the two parts of the stomach, diffusion of the saliva and the soluble constituents of the food on the one hand and of the gastric juice and the products of gastric digestion on the other must constantly and rapidly take place throughout the stomach, just as would occur if materials of similar consistency were poured consecutively into a tall

³ In the majority of post-mortem specimens, however, no such depression is found, as the stomach is generally resting immediately before death. Moreover, unless special precautions are taken the muscular coat of the stomach becomes completely relaxed soon after death.

glass jar. Moreover, the respiratory movements produce some mixing of the gastric contents, which can also be seen with the X-rays to be thoroughly churned by strong contractions of the abdominal muscles. Thus even moderate exercise, by increasing the abdominal and respiratory contractions, would cause the contents of the upper and lower parts of the stomach to be mixed together. Lying down has a still greater effect, as can be easily seen with the X-rays. Lastly, the heavier articles of food tend to sink to the most dependent part of the stomach, whereas lighter food, such as oil, tends to rise to the surface. This is well seen when a bismuth salt is given in water at the end of an ordinary meal: it can be observed with the X-rays to fall rapidly to the bottom of the stomach.

The food taken at the beginning of a meal reaches the pyloric end first, and that taken last is at first uppermost. Pepsin is secreted in all parts of the stomach, hydrochloric acid mainly or entirely in the cardiac end. Some hydrochloric acid is carried with the first part of the meal to the pyloric end. In the latter the food and gastric juice are being constantly mixed by peristalsis. In the cardiac end there is no peristalsis, so the peripheral part of the food is most acid and the central part may remain for a long time alkaline and undergo salivary digestion. But these three divisions—pyloric moderately acid, peripheral cardiac very acid, central cardiac alkaline—are constantly altering and are quite indefinite, as the hydrochloric acid as soon as it is secreted and the soluble constituents of the food and the products of its digestion are always passing by diffusion into the other parts of the stomach, and the movements of the diaphragm, abdominal muscles, and body as a whole tend to mix together the contents of all parts of the stomach. By Sick's method most of the contents of the cardiac end are removed; these when mixed are more acid than the pyloric contents, although the central part may be alkaline.

The stomach is thus no more definitely divided into two parts functionally than anatomically. Owing, however, to its outlet being at the opposite end to its inlet, and to the peristalsis only occurring at one end, whilst hydrochloric acid is chiefly secreted at the opposite end, the consistency and composition vary in different parts in spite of the mechanical and physical factors, which continually tend to make the whole of the contents homogeneous.

These facts are of great importance in estimating the clinical value of gastric analyses, as Prym pointed out after the publication of Grützner's observations. In order that comparable results may be obtained, it is essential that the stomach should be completely evacuated after a test meal and that all the material obtained should be thoroughly mixed. Otherwise a portion may be examined which contains no free hydrochloric acid, although free hydrochloric acid is present in other portions, and similar mistakes may be made with regard to the quantity of 'active' hydrochloric acid, pepsin, and the products of gastric digestion present. If the patient be told to contract his abdominal muscles, and to strain as soon as the tube has reached his stomach, it is generally quite easy to obtain every trace of the gastric contents without introducing any water.

The evacuation of the stomach. In the foetus and child the pyloric canal is often found still closed after death. This is seen in an exaggerated degree in the hypertrophic pyloric stenosis of infants. In the normal adult it is generally more or less expanded in post-mortem specimens, but its cavity never merges into that of the pyloric vestibule without an indication of the subdivision being found in the interior of the organ.

During life the pyloric canal is probably always closed by the tonic contraction of the sphincter, variations in which regulate the passage of the gastric contents into the duodenum. Even when relaxed for the passage of food, the canal is so narrow that either no shadow is cast by the X-rays of bismuth passing through it (Holzknecht) or, as I have occasionally observed, a very fine line joins the gastric and duodenal shadows (Fig. 7, III and IV).

Peristalsis is therefore required not only for mixing the food with the gastric juice, but also for pressing even finely divided particles through the pylorus; in the case of larger particles very strong peristalsis is required to overcome the resistance. Peristalsis, however strong, could not push the gastric contents through the pylorus unless the contraction was sufficiently deep to shut off the extreme pyloric end of the stomach almost completely from the rest, as it would otherwise simply produce a slight rise in the general intragastric pressure, which would be no greater at one end of the stomach than the other. But, as I have already pointed out, X-ray observations show that the peristaltic wave, when it approaches the pylorus, forms a more or less complete division across the stomach, so that the further passage of the wave and the contraction of the longitudinal muscle-fibres produce a very considerable pressure in this part of the stomach, which is sufficient to overcome the resistance offered by the pyloric canal.

Moritz (1901) was the first to show by experiments on animals that water drunk alone when the stomach is empty rapidly leaves it, and X-ray observations have proved that the same occurs in man with water to which a bismuth salt has been added. Consequently, if drunk half an hour before meals, water does not dilute the gastric juice and interfere with digestion.

Fluid taken during meals leaves the stomach much less rapidly; Leven and Barret found that 200 c.c. of water disappear completely from the stomach in about twenty minutes, but if taken after food—even so little as a few mouthfuls of bread—a considerable portion is still present in the stomach after half an hour. Consequently fluid taken with meals dilutes the gastric juice and adds to the bulk and weight of the gastric contents. Many cases of dyspepsia, therefore, especially those in which there is deficient secretion of gastric juice or atonic dilatation, are greatly benefited by restricting the quantity of fluid drunk during or immediately after meals. In most cases the best time to take the fluid is half an hour or an hour before meals.

Raw egg-albumin leaves the stomach as rapidly as water (Carnot and Chassevant), and, like water, it gives rise to no secretion of gastric juice. Other fluids, such as milk, bouillon, and beer (Moritz), which produce a flow of gastric

juice, leave the stomach much more slowly. It is probable, therefore, that the tone of the pyloric sphincter is feeble when the stomach is empty, and the muscle contracts on the introduction of any food which has the property of exciting gastric secretion. This perhaps accounts for the fact that albumin water is often kept down by infants with gastric disturbance, which causes them to vomit diluted or peptonized milk, both of which remain for a comparatively long time in the stomach.

Although the tone of the pyloric sphincter is increased as soon as food which has the power of exciting the secretion of gastric juice is introduced into the stomach, Tobler found by experiments on animals with duodenal fistulae that everything which came through the pylorus was acid in reaction, and Cannon (1907) found that the passage of food into the duodenum of cats begins only at the moment when the contents, whether they be mainly carbohydrate or mainly protein, become acid. Cannon further showed that the introduction of acid into the stomach causes the pyloric sphincter to relax, whereas neutralization of the acid contents delays evacuation. In some later observations with Hedblom he found that potato acidified to 0.25 per cent. HCl left the stomach much faster, to 0.5 per cent. rather faster, and to 1 per cent. no faster than ordinary potato. A neuro-muscular mechanism probably exists at the pylorus similar to that which regulates the cardia in swallowing, relaxation of the sphincter occurring, under certain conditions, on the arrival of each peristaltic wave at the pylorus. The observations of Tobler and Cannon show that in animals the necessary condition is that free hydrochloric acid should be present in the pyloric part of the stomach. This is certainly not the case in man, in whom relaxation occurs before free hydrochloric acid is present, as I have repeatedly seen food begin to leave the stomach within two minutes of its entry, long before the hydrochloric acid (according to Sick) has had time to appear. But the degree of relaxation of the pyloric sphincter on the arrival of each peristaltic wave and the consequent rate of discharge of the gastric contents doubtless increase with the quantity of free hydrochloric acid present in the pyloric part of the stomach.

These facts explain why a carbohydrate meal begins to leave the stomach earlier than a protein meal, as the former does not combine with hydrochloric acid, whereas proteins combine with the first portion secreted, with the result that a longer period must elapse before free acid is present. Fats inhibit the secretion of gastric juice, so that their presence in a meal postpones the appearance of free acid and consequently the relaxation of the pylorus. This explanation is confirmed by Cannon's (1898) observation that carbohydrates, moistened with an alkaline solution, which checks the flow of gastric juice as well as neutralizing the acid secreted, leave the stomach less rapidly than they would do otherwise, and that acid albumin, which is incapable of combining with any more acid, passes through the pylorus at an earlier period than ordinary protein.

The discharge of carbohydrates from the stomach not only begins sooner, but it also continues more rapidly than that of proteins and fats, the discharge

of either of the latter when present alone taking twice as long as the discharge of an equal quantity of the former.

Owing to the different rates of discharge of different food-stuffs, a meal composed chiefly of carbohydrates, which are digested by pancreatic, but not by gastric, juice, leaves the stomach more rapidly than one composed chiefly of proteins, which are digested by pepsin as well as by trypsin. As most of the food remains in the stomach until it is acid, all of the chyme which reaches the duodenum gives rise to the production of secretin and consequently stimulates the secretion of pancreatic juice and bile. Cannon has shown in a freshly excised stomach that acid produces relaxation of the pyloric sphincter by its action on the mucous membrane in the immediate neighbourhood. This explains why protein given after carbohydrate does not materially check the rapid discharge of the latter from the stomach, although it combines with the hydrochloric acid secreted in the cardiac end, and that carbohydrate given after protein does not hasten the slow discharge of the latter, although it does not combine with the hydrochloric acid which accumulates in contact with the mucous membrane of the fundus. If the reflex originated at the fundus, the pylorus would relax at once, as most of the hydrochloric acid is secreted in this part of the stomach, where there is no peristalsis, so that there is always some acid in contact with the mucous membrane. On the other hand, the secretion of the mucous membrane near the pylorus is only feebly acid, most of the acid which reaches it being carried from the fundus. Owing to the thorough mixing which occurs in the pyloric part of the stomach, free hydrochloric acid is not present until peptic digestion of protein has had time to commence.

A mixture of protein and carbohydrate leaves the stomach at a rate intermediate between that of either taken separately. Fat, when added to protein or carbohydrate, causes delay in the emptying of the stomach. This explains the slowness of the digestion of pork and veal compared with beef and mutton. Protein taken after carbohydrate leaves the stomach at the normal rate, but carbohydrate taken after protein leaves more slowly than when taken alone.

The relaxation of the pyloric sphincter on the arrival of a peristaltic wave is inhibited by certain reflexes. The most important of these result from stimuli to the duodenal mucous membrane, as Hirsch and von Mering discovered independently by means of artificial duodenal fistulae. Pawlow and his fellow workers showed that the stimulus is mainly chemical and not mechanical, as Hirsch and von Mering believed. Thus injection of gastric juice or 0.1 per cent. of hydrochloric acid through a fistula into the duodenum caused the flow of gastric contents through the pylorus to cease, but water and neutral or alkaline saline solutions had no such effect.

The result of this chemical reflex is that no more acid chyme enters the duodenum until that which arrived immediately before is neutralized by the pancreatic juice and bile, the secretion of which is called forth by the presence of acid in the duodenum. This mechanism is of great importance, as it keeps

the reaction of the small intestine below the opening of the common bile duct neutral or alkaline, and so allows digestion by the pancreatic ferments to proceed, and at the same time it protects the mucous membrane from the liability to ulceration which is associated with the acid reaction of the contents of the stomach and the first part of the duodenum.

Pawlow found that the stomach empties itself abnormally slowly if the neutralization of the chyme is prevented by the escape of the pancreatic juice through a fistula; this may be one cause of the digestive disturbances which follow obstruction to the common bile duct in man. On the other hand, Tobler found that if the acid contents of the stomach were allowed to leave the duodenum by a fistula as soon as they had passed through the pylorus so as to prevent its reflex closure, the gastric digestion of meat continued for a shorter period and was consequently much less complete than under normal conditions. Cannon has pointed out, however, that the initial discharge of food rich in protein is late even under these circumstances, as the initial retardation is due to influences at work in the stomach and not in the duodenum.

Von Mering discovered that injection of milk into the duodenum caused the passage of the gastric contents through the pylorus to cease until the milk had disappeared into the next part of the intestine. He looked upon this as the result of a mechanical reflex, but Pawlow proved that it depended on the presence in the milk of fat, which he showed produces a similar reflex to hydrochloric acid when it comes into contact with the duodenal mucous membrane. As fat inhibits the flow of gastric juice, and as the tone of the pyloric sphincter appears to be well marked only if food which excites the flow of gastric juice is present in the stomach, the presence of fat in the stomach is associated with a relaxed pylorus. Hence, in spite of the fact that the presence of fat in the duodenum causes the regular jets of gastric contents—which would otherwise occur each time a peristaltic wave reaches the pylorus—to cease, single drops still issue without intermission from the pylorus. The closure of the pylorus is also not sufficiently tight to prevent the frequent reflux of oil mixed with bile, pancreatic juice, and intestinal juice into the stomach (Boldireff). Advantage has recently been taken of this remarkable occurrence by giving a small quantity of oil by mouth when the stomach is empty in order to obtain a specimen of the pancreatic juice and bile, when it is desired to find whether they are normal. For the oil inhibits the secretion of gastric juice, and as soon as a little reaches the duodenum it excites the flow of bile and pancreatic juice, with which some of it regurgitates into the stomach.

Inhibition of pyloric relaxation also occurs when the mucous membrane of the pyloric part of the stomach comes into contact with anything which might injure the duodenal mucous membrane owing to its mechanical or chemical properties. Thus Cannon found that chyme ceased to pass through the pylorus for a short period after a peristaltic wave had carried against it a solid pellet, which had been swallowed with the food. Consequently insufficiently chewed masses of food remain in the stomach until all the fluid and semi-fluid contents

have left, so that more time is given for the gastric juice to soften them and for the gastric peristalsis to break them up. To this extent only does the pylorus act as a filter, which allows fluid to pass into the duodenum, whilst larger masses of solid food are retained for a time in the stomach.

More recently Hedblom and Cannon have shown that hard particles are not only retained in the stomach longer than softer food, but that the evacuation of the latter is also delayed as a result of their presence. Coarse branny food, however, stimulates peristalsis so powerfully that it is forced through the pylorus more rapidly than chemically similar food of finer texture. Thus wholemeal bread leaves the stomach sooner than an equal quantity of white bread.

Johannes Müller found that tea, milk, and bouillon left the stomach much more rapidly when introduced at the body temperature than when cooled to 5°C. or heated to 50°C. He found moreover that the temperature of the food rapidly approached that of the body. Thus 500 c.c. of tea introduced at 50°C. was cooled to 41°C. in three minutes and 38°C. in nine minutes, and the same volume of tea introduced at 5°C. was warmed to 23° in three minutes and 32° in nine minutes. However, all the cold tea had left the stomach before sufficient time had elapsed for it to reach the body temperature. Under normal conditions the passage of hot and cold food through the mouth and oesophagus brings it to a temperature which more nearly approaches that of the body than the tea in Müller's experiments. The protective mechanism, which he proved to exist, by means of which the pylorus retards the evacuation of hot and cold food, must therefore generally be sufficient to prevent chyme entering the duodenum in any considerable quantity until its temperature is almost the same as that of the body. Müller's observations, which were made on healthy young men, lose none of their importance on account of the contrary results of the experiments performed on dogs and cats by Schüle, Roeder, and Hedblom and Cannon, who found that cold and hot fluids often leave the stomach more rapidly than fluids at the body temperature. Perhaps in animals the stimulating action of heat and cold on peristalsis may sometimes be sufficient to overcome the protective mechanism of the pylorus. Moreover the protective mechanism is less important and has less time to act in the small stomach of the cat and dog, as the change in temperature of the food to that of the body would be much more rapid than in the much larger stomach of man.

Distilled water and anisotonic saline and sugar solutions generally remain longer in the stomach than isotonic solutions (Carnot and Chassevant, Otto). This is probably also due to inhibition of pyloric relaxation. Consequently the chyme, when it reaches the duodenum, is much more nearly isotonic with the tissue-fluids than when it reaches the stomach. The change is brought about in part by the secretion of fluid rich in salt in the case of hypotonic solutions and distilled water, and by the secretion of ordinary gastric juice in the case of hypertonic solutions. Osmosis and diffusion undoubtedly help in both cases. The change is much less rapid in hypertonic than in hypotonic solutions, but

even very concentrated solutions become almost isotonic before their evacuation from the stomach is complete.

Thorough mastication divides the food into fine particles, dilutes it with saliva, and brings it to the body temperature. Under ideal conditions, therefore, the food is so altered in the mouth that comparatively little remains to be done in the stomach in order to prepare it for transmission into the duodenum.

By observations on himself A. Schmidt showed that massage accelerates the discharge of the gastric contents. Exercise immediately after food slightly increases the rapidity of evacuation, but if it is sufficiently strenuous to cause considerable fatigue, the discharge is said to be retarded.

The nervous control of the gastric movements and the pylorus. The muscular coats of the stomach receive fibres from the vagi and from the sympathetic nervous system. The vagal fibres end in connexion with the ganglion-cells of Auerbach's plexus, which is situated between the circular and longitudinal muscular coats, and the sympathetic fibres, which originate in the lower dorsal region of the spinal cord and are conveyed by the splanchnic nerves, have their cell station in the coeliac plexus.

Stimulation of the splanchnic nerves causes a slight diminution in the tone of the stomach and the pylorus and inhibits peristalsis, whereas stimulation of the vagi greatly increases the tone of the stomach and pylorus and renders peristalsis more active after temporarily inhibiting it.

In spite of the fact that it possesses this double nerve-supply, the stomach can perform its functions to a great extent independently of the central nervous system. Thus peristalsis occurs in excised stomachs, which have been kept moist and warm, although changes in the tone of the pylorus have never been observed under these conditions. Aldehoff and von Mering found that the tone and peristalsis of the stomach and the pyloric reflexes remained normal for months after both vagi had been cut just below the diaphragm and also after destruction of the coeliac plexus or division of the splanchnic nerves. These results were confirmed by Cannon by X-ray observations on the stomachs of cats after section of the vagi and the splanchnic nerves.

Magnus found that isolated strips of intestinal muscle are only capable of spontaneous rhythmical contractions if the local nerve-plexus is removed with them. It is possible that the motor functions of the stomach, like those of the intestines, depend mainly on reflexes, which have their centre in the nerve-cells of Auerbach's plexus. The duodenal control of the pylorus also depends on a local reflex, as it is abolished by cutting through both muscular coats of the duodenum as close as possible to the pylorus, in such a way that Auerbach's plexus is severed, the duodenum and stomach being only united by mucous membrane.

There is, however, no doubt that under certain conditions the movements of the stomach can be directly or reflexly inhibited by the central nervous system. Cannon found that peristalsis in his cats ceased when they were excited or angry, and Pawlow showed that reflex inhibition was produced by stimulation

of various sensory nerves. The inhibition occurred when both vagi were cut, so that it must be due to impulses which are carried by sympathetic nerve-fibres. The pylorus is affected in a similar way: thus the normal relaxation which occurs on the arrival of each peristaltic wave was found by Carnot to be inhibited by fear or anger and by painful stimulation of sensory nerves.

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SOME MORBID HISTOLOGICAL CHANGES MET WITH IN THE LYMPHATIC GLANDS: ESPECIALLY IN CON- NEXION WITH THE FORMATION OF 'HAEMOLYMPH' GLANDS

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With Plates 12 and 13

SINCE H. Gibbes and later W. F. Robertson first drew attention to the existence of 'haemolymph' glands in man and animals, these structures have been investigated by several observers, and more particularly by Scott Warthin. This author described two varieties of these glands, to which he gave the names of 'splenolymph' and 'marrow-lymph' glands. He described certain structural differences between the two varieties and considered their functions as mainly haemolytic and haemopoietic respectively. He found transitional forms between these glands and ordinary lymphatic glands, but regarded them as specialized structures.

The object of the present work was to investigate the histological changes found in the lymphatic glands in disease, the occurrence of haemolymph glands in the human subject, and their claim to special classification.

Selection of Material.

The cases from which material was obtained were selected from among the fatal cases of a large general hospital during a period of two and a half years. Naked-eye examinations of the main groups of lymphatic glands were made during a very large number of autopsies and the selection was made with a view to obtaining a number of examples of each of the main groups into which diseases may be roughly divided, and also of including those cases in which changes in the lymphatic glands were visible to the naked eye.

Any attempt to classify the cases into groups is necessarily rough, as many cases fall naturally into more than one group. The first class comprises examples of acute general infection for the most part of known bacterial origin, and includes 15 cases of generalized infection by the commoner pyogenic cocci, 6 of pneumococcal infection (mainly lobar pneumonia), 3 of epidemic cerebrospinal meningitis, 5 of typhoid fever, and 7 of diphtheria. With these are

included cases of varicella, measles, pyaemia due to the influenza bacillus, and a few examples of general infection or toxæmia of unknown origin. In a large majority of this group the causative micro-organism was isolated and recognized during life or subsequently. A second class consists of cases of acute infection in which the infective process was clinically confined to some particular region or organ. Under this heading are included local suppurative processes, peritonitis, endocarditis, dysentery, &c. Cases of chronic infection or sepsis of long standing form a third group, the majority being examples of chronic suppurative processes. The fourth class contains examples of cases showing evidence of severe anaemia. It includes 6 cases of pernicious anaemia, an equal number of severe secondary anaemia (due to prolonged hæmorrhage, carcinoma of stomach, &c.), and cases of lymphæmia, myelæmia, and generalized sarcoma. The cases in this series all showed profound blood changes, but naturally examples from the preceding classes presented equally marked changes in the blood. Other cases which do not fall into the preceding groups bring up the total to over 80 cases of human disease.

In cases of generalized disease a number of glands were removed from each of several situations, usually three or four, including the locality where 'haemolymph' glands are commonly found, and also from more superficial groups, e.g. the inguinal or axillary. Where a local focus of disease existed, glands were taken from those groups anatomically connected with the diseased area and also from more distant situations. In certain cases careful dissections of the retro-peritoneal tissues were made and a large number of glands isolated and removed. In a considerable proportion of the cases the spleen and bone marrow were also subjected to microscopical examination. The cases examined included patients of all ages, the majority, however, being young subjects.

Technique.

Glands were obtained from the post-mortem room¹ and, in the case of animal experiments, as soon as possible after the animal had been killed, and entire glands, if small, or portions of larger ones were fixed in salt formalin solution or weak spirit. Sections were cut in paraffin. Mayer's hæmalum followed by eosin was used as a routine stain. For detailed cytological examination, sections were stained by Leishman's stain, and after differentiation in very weak acetic acid were treated with a solution of alcoholic eosin dissolved in absolute alcohol. This method, though somewhat lengthy, was used as a routine method in all cases. It was especially useful in demonstrating the presence of red blood corpuscles. The staining affinity of these cells was often much reduced and ordinary staining processes sometimes failed to show them, or did so very imperfectly, when the above method showed their presence in

¹ Autopsies were made in all cases within 24 hours of death, and the bodies had invariably been kept in a freezing chamber.

considerable numbers. Various other special stains were employed for the demonstration of fibrin, bacteria, certain degeneration products, &c.

Film preparations were made of the fluid expressed from the glands and these were stained by Leishman's stain. Differential counts were made of the cells present on these films; usually five hundred cells were counted, but in a few cases more, in some less. In a number of cases films were fixed while still wet and stained with Scharlach R. for the demonstration of intracellular fatty change.

On the Occurrence of Haemolymph Glands in the Human Subject.

Accepting the definition of a haemolymph gland as one which possesses a sinus containing blood instead of lymph, it would appear that in pathological conditions in the human subject their occurrence in large numbers is almost universal. In only two or three of the large number of glands examined did I fail to find red blood corpuscles in one or more of the sinuses. The amount of this blood varied within the widest limits. In some cases the sinuses were widely dilated and filled with blood, in others the amount of blood was very small. In the latter variety the blood is sometimes difficult of demonstration. The corpuscles are often deficient in haemoglobin and require special staining methods to make their presence evident in sections. For this purpose I have found Leishman's stain followed by eosin very useful. Such glands were usually present in greatest number along the course of the large vessels in the abdomen, thorax, and neck, but were frequently found in more superficial positions. Thus the axillary, inguinal, or superficial cervical glands often showed the presence of blood sinuses, sometimes to a marked extent. The locality in which such glands were found to be most numerous varied with the site of any local lesion, where such lesion existed. For example, in a case of old-standing tuberculous disease of the hip-joint with secondary septic infection of the joint, while all the glands examined from the neck, thorax, and abdomen were enlarged and red, and on microscopic examination proved to be 'haemolymph' glands, these changes were much more advanced in the glands from the pelvic cavity and about the bifurcation of the abdominal aorta. Again, in a case of septicaemia without any external lesion, the only lesion found after death was widespread infarction of the spleen. Here haemolymph glands were present in abundance in the region of the spleen and stomach, smaller and less numerous along the abdominal aorta, while the glands along the course of the iliac vessels showed little change.

In a few cases where haemolymph glands were present in large numbers I have removed and examined all the easily found lymphatic glands of the same group and have found them all to show a practically identical condition. It appears then that every lymphatic gland is a potential haemolymph gland. The experimental production of such glands in the guinea-pig is easy of accomplishment. A number of these animals received intraperitoneal inoculations of various toxic substances (living pathogenic bacteria, diphtheria toxin,

oxalic acid, distilled water). The guinea-pigs were subsequently killed at varying intervals of time. The glands from the abdominal cavity and also from more distant localities almost invariably showed the changes characteristic of haemolymph glands to a greater or less degree. These changes were most evident in animals which were allowed to live for 10-12 hours or more, but were well marked in some cases in one or two hours. Dudgeon, Panton, and Ross have produced similar changes by the inoculation of haemolytic sera. In cases of generalized disease without obvious local lesions, such as acute septicaemia, pernicious anaemia, and allied conditions, the greatest number and most marked examples of haemolymph glands occur along the course of the larger vascular trunks. This fact has been recorded by previous observers and the present findings tend to confirm it. The lymphatic glands in such situations appear to be especially prone to undergo those changes which constitute them haemolymph glands, and when haemolymph glands have been found in apparently normal individuals it is in such situations that they have proved to be present.

There is little recorded evidence as to the extent to which haemolymph glands occur in perfectly healthy human beings. Opportunities for such investigation are rare. During the course of this work a careful dissection was made of the retroperitoneal tissue of the abdomen, from a healthy man who met with a rapidly fatal accident. All the lymphatic glands in this situation visible to the naked eye were removed and a large number examined microscopically. In none were changes present to warrant their classification as haemolymph glands. A similar examination was made of two fetuses which had died during delivery at about full term with similar negative result. These findings are only partially conclusive, since it is well known that many of the points of lymphoid tissue present in the abdominal fat are too small for naked-eye recognition. They lend some weight, however, to the view that while haemolymph glands are nearly always to be found in morbid conditions in the human subject, they are not universally present in the normal subject, or if so are only demonstrable with difficulty.

Since all stages of transition exist between the normal lymphatic gland on the one hand and the well-marked haemolymph gland on the other, and since every lymphatic gland is liable to undergo this transition, it seems unreasonable that the human 'haemolymph' glands should be classed in a separate category, nor does it seem necessary that the changes found in the lymphatic and haemolymphatic tissue in disease should be described under separate headings.

The Haemolymph Glands of the Pig.

For purposes of comparison, a detailed study was made of the haemolymph glands from one of the lower animals in which they are known to occur and to be of convenient size. The domestic pig was the animal selected, and glands were obtained from three healthy pigs immediately after death. These glands are numerous in the retroperitoneal fat and vary in size from minute red points

to structures exceeding an inch in length. They are soft and friable, intimately connected with the fat in which they lie, deep red in colour, and extremely vascular. On microscopical examination they are seen to possess a very thin capsule, and in some cases a distinct capsule cannot be said to exist, the peripheral sinus of the gland being directly contiguous with the periglandular fat and the cellular tissue of the sinus spreading between the contiguous fat cells. This condition much resembles that seen in the marrow of the long bones at the junction of cellular and fatty marrow. The peripheral sinus is wide, and in some instances a section through a gland shows an enormous sinus surrounding one or two small central areas of lymphoid tissue. The structure of the sinus consists of a ground-work of branching connective-tissue cells and is packed with red blood corpuscles. In those glands where the lymphoid tissue is small in amount, sections give the appearance of a sea of blood with a small island of lymphoid tissue in the middle.

The lymphoid tissue proper, as stated above, varies much in amount. The lymph follicles show prominent and sharply-defined germ-centres, and are separated from one another by wide blood sinuses continuous with the peripheral sinus. Throughout the gland, both in the sinuses and among the lymphocytes in the lymph follicles, are large numbers of cells with oxyphilic granules. These cells are both finely and coarsely granular, and their nuclei show all stages of transition from a single round nucleus to that of the typical polymorphonuclear cell.

Of especial interest are certain small islets of cells which occur in the midst of the blood in the sinuses. They are sharply defined from the surrounding red blood corpuscles, and are formed from aggregations of various types of blood cells. One such focus will contain, perhaps, fifty closely-packed normoblasts, another a clump of myelocytes, neutrophilic or eosinophilic in granulation, while yet others are made up of aggregations of polymorphonuclear cells (Fig. 1). Mitotic figures may be seen in the cells of these islets. Another cell of interest to be seen in the sinuses, though only occasionally, is a large cell closely resembling the megakaryocyte of the bone marrow. Evidences of red corpuscle destruction are very few, but in film preparations from the glands an occasional endothelial cell with the included remains of an erythrocyte may be met with.

The above appearances would seem to suggest that a part, at least, of the function of these glands in the pig is concerned with the formation of blood cells, red and white, and they are described at some length as they differ materially from the condition found in any human haemolymph glands examined in the course of this investigation.

On some General Changes met with in the Lymphatic Glands.

Increase in size and number of the lymphatic glands throughout the body was constantly met with in a large variety of acute and chronic diseases.

With these changes was usually associated change in colour. In twenty-one cases the large number of big red glands seen at autopsy was very striking. In such cases they were present in the usual glandular situations and studding the abdominal and mediastinal fat. The list is composed mainly of examples of chronic sepsis of some standing and the severe anaemias, but also includes instances of acute infectious processes, e.g. pneumonia, cerebro-spinal meningitis, enteric fever, and diphtheria. Several observers have pointed out the intimate relation existing between adipose and lymphatic tissue and the rapid metaplasia of the former to the latter in case of need. A replacement of lymphatic tissue by fat is also commonly seen in the glands.

The change in colour was found to be due to one or more of several causes: increased vascularity, either of the capsule or throughout the gland substance, haemorrhages, the presence of blood in the sinuses, or pigmentation. The dark red colour of a gland may be due to any or several of these factors; to which, can only be decided by microscopical examination.

General increased vascularity of the lymphatic glands was commonly found, and was as a rule most marked in the acute infective conditions where it is an early change. It was often present to a striking degree, so that the main part of sections of such glands was occupied by dilated capillaries without the lymphoid tissue necessarily showing any cellular changes of acute inflammation. In other cases, the increased vascularity could be ascribed to passive congestion. Haemorrhages, usually of small size, were occasionally present, usually in those diseases where capillary haemorrhages are known to occur. Occasionally a gland was met with which from one or other of the above causes had been converted into a thin-walled blood cyst. The presence of blood in the sinuses was, as stated above, of practically constant occurrence. The amount varied within the widest limits. As a general rule, the most marked blood sinuses were found in cases of chronic infection or fatal anaemia, but this was by no means invariably so, as many excellent examples were found in acute infective conditions and among the experimentally inoculated animals. In this situation the red blood corpuscles frequently showed all stages of destruction and disintegration, and were occasionally seen to be agglutinated into clumps. At times the sinuses were mainly filled with a homogeneous serum-like substance staining lightly with eosin. Phagocytosis of the red blood corpuscles by the proliferated endothelial cells of the sinuses is the most striking feature of such glands and has long been recognized as one of the important functions of the lymphatic glands. It is seen after death in a large number of different conditions. Its extent varies greatly in individual cases of the same disease and in different glands from the same individual. Examination of the red bone marrow and spleen in many cases showed evidences of a similar haemolysis.

The degree of pigmentation varied with the amount of haemolysis present. Such pigment was usually yellow or light brown in colour, and was usually confined to the sinuses or their immediate vicinity, though sometimes seen in the cells at the germ centres. A reaction for free iron was very variable, and in the

majority of cases not obtained, though occasionally the sections showed the presence of a large amount of free iron.

Among other general changes may be mentioned fibrosis, which was very frequently met with in varying degree, and the occurrence of areas of hyaline material in the follicles of the gland. This hyaline deposit, as is described below, usually occurs first among the cells at the germ-centres, but in time may spread through the whole of a follicle.

Histological Changes at the Germ-centres.

Marked histological changes are met with at the germ-centres of the lymphatic glands in the course of a great variety of infective and non-infective diseases. In fact, these portions of the gland tissue appear to be especially sensitive to the action of any morbid agent, whether bacterial or toxic. They rapidly undergo degeneration and disintegration, and in a great majority of the fatal cases of acute or chronic disease examined they presented evidences of marked degeneration and were recognizable only with difficulty.

In the glands of only seven out of the total number of fatal cases of disease in human beings were these bodies a prominent feature of the sections.

These seven cases were made up as follows:—

1. Child, aged 2. While suffering from varicella fell from a window, sustaining injuries which caused death in a few hours.
2. Man, aged 23. Septicaemia of three weeks' duration. Died suddenly from septic thrombosis of both middle cerebral arteries.
3. Child, aged 4 months. Death in a few hours from onset of acute epidemic cerebro-spinal meningitis.
4. Child, aged 2. Fatal dysentery of a few days' duration.
- 5, 6, 7. Three cases of laryngeal diphtheria, dying a few hours after tracheotomy.

All of the seven were instances of rapidly fatal infection or of sudden death in the course of an infective disease. The earlier histological changes at the germ-centres of the lymphatic glands were studied in a series of guinea-pigs, which received intraperitoneal inoculations of *Bacillus coli* and were subsequently killed at varying intervals. Other guinea-pigs received intraperitoneal inoculations of diphtheria toxin, nucleic acid, and *Staphylococcus aureus*. In these experiments glands were taken from two situations; the mesenteric glands were examined in all cases, and also glands from the thoracic cavity (the glands at the tracheal bifurcation), or from the inguinal region. Within two hours of inoculation well-marked changes are to be seen at the germinal centres of these glands. They consist of an increase in size of the whole centre, together with a great increase in the number of mitotic figures in the large endothelial cells of which the germ-centre is composed. Increased phagocytosis by these cells is visible, and they contain red blood corpuscles, light-brown pigment, and

the remains of leucocytes and nuclear debris. At times entire lymphocytes are seen to have been ingested. Often the germ-centre shares in the general vascularization of the gland, and a central arteriole is evident. These changes rapidly become more marked, and in the series of animals investigated they reached their height at the end of six hours. Precisely similar changes were found, not only in the mesenteric glands, but also in those from more remote regions, and in a parallel series of guinea-pigs which had received inoculations of nucleic acid in place of the living bacilli the germ-centres presented an almost identical appearance.

Degenerative changes appear very rapidly. At the end of six hours many of the cells of the germ-centres were ragged in outline and their nuclei showed signs of disintegration. Some of the cells stained ill, and the appearance of areas of hyaline structureless material was noticed between and among the cells. After ten hours the germ-centres were considerably smaller and largely composed of this hyaline material, together with a few ragged-looking cells and small masses of pigment.

In the human cases where the glands contained prominent germ-centres very similar changes were found. In some instances the centres were greatly increased in diameter and occupied more than a field of the microscope with a $\frac{1}{8}$ th inch objective and low-power eyepiece. Increased mitoses and phagocytosis, together with signs of commencing cellular degeneration, were common to all the cases and varied only in degree, and the germ-centres were often very vascular.

In the vast majority of cases examined the appearances were strikingly different. With the exception of the above-mentioned seven cases the changes found at the germ-centres were those of degeneration. In many instances these bodies were recognized only with difficulty and sometimes they had completely disappeared. When present they contained comparatively few cells and were small in size. In place of the large pale staining cells present in the normal gland they contained a few ragged and shrunken endothelial cells or a few lymphocytes, together with a varying amount of a hyaline or fibrous material. Sometimes they were represented by circular hyaline areas with few or no included cells. In some cases of long-standing sepsis and in a case of lymphadenoma these hyaline areas gave a positive reaction for amyloid.

A number of glands were examined which had been removed during life on account of chronic enlargement in connexion with septic processes. A majority of these showed well-marked hypertrophy of the germ-centres and contrasted strongly with the condition present in most of the glands obtained from the post-mortem room.

Observations on the Cellular Elements of the Glands.

A. *Nucleated red cells.* The presence of nucleated red blood corpuscles in the lymphatic glands of man and other animals has frequently been observed and a part in red-cell production assigned to these structures. Retterer con-

cluded that haematopoiesis was an important function of these glands. Scott Warthin states, in speaking of the marrow-lymph glands, that 'though these glands undoubtedly form red blood corpuscles under certain pathological conditions, I have not yet found any absolute evidence that they do so under normal conditions'. This author found nucleated red cells in considerable numbers, at times showing mitotic figures, in the glands from cases of severe anaemia. The presence of such cells in a tissue does not of course prove their formation at that site, and the possibility that such cells are only deposited from the blood stream must always be considered. In the present investigation a large number of glands from patients dying with signs of grave anaemia have been examined with special reference to this question. Particular importance was attached to a careful search through stained films of the gland juice, since the identification of nucleated red cells in sections of richly cellular lymphoid tissue is often a matter of some difficulty.

The presence of such cells, except in occasional very small numbers, has proved of rare occurrence. In only three instances were erythroblasts in large numbers found in film preparations and sections of the glands. These were cases respectively of pernicious anaemia, generalized sarcomatosis, and acute lymphatic leukaemia. The first case was a typical example of the disease, and the blood contained a considerable number of erythroblasts. The marrow was hyperplastic and showed many nucleated red cells. A differential count of cells present in the lymphatic gland juice showed a very large proportion of nucleated red cells, in fact their number in proportion to the total number of red cells seen in the films was noticeably large. Sections of glands from this case, moreover, showed a striking resemblance to bone marrow.

In the other two cases the glands also contained erythroblasts in large numbers. In both the blood contained a very large number of nucleated red cells. The marrow in both was hyperplastic and showed the presence of many of the same cells, though in both this tissue was infiltrated, in the one case by cells of the growth, in the other by lymphoid cells.

These findings tend to confirm the belief that the glands may vicariously assist or replace the bone marrow in so far as this particular function is concerned.

Among the cases of severe anaemias were three in which the bone marrow either failed to show hyperplasia or was grossly degenerated. Two were examples of pernicious anaemia in which this tissue had undergone marked degeneration, the other was an instance of a fatal unclassified anaemia with obvious hypoplasia of red marrow. Nucleated red cells were found in small numbers in the glands from these patients, but in all three the blood contained very few erythroblasts. In the last-mentioned case, however, portions of the glands presented a striking histological resemblance to bone marrow. No instance was met with in which nucleated red cells were found in appreciable numbers in the lymphatic glands without the presence of these cells in considerable number in bone marrow and blood.

Turning to cases of severe anaemia of comparatively short duration, the list includes four cases of gastric or duodenal ulceration with death as the result of haemorrhage. In none of these was there evidence of haematopoiesis in the lymphatic glands, though the red marrow in each instance contained striking numbers of normoblasts.

Search through sections of a number of glands from all the above cases has failed to demonstrate the presence of aggregations of nucleated red cells, such as may be seen in an actively erythroblastic bone marrow or such as are described elsewhere in this paper as occurring in the haemolymph glands of the pig.

In conclusion, it would seem that histological evidences of this haemopoietic function of the lymph-glands are only to be seen in man in comparatively rare instances, and that when exercised the reaction is as a rule secondary to a similar reaction of the bone marrow.

B. *The lymphocytes.* With the early enlargement of the lymphatic glands, which occurs in so many acute infective processes, there is an obvious actual increase in the number of these cells. The same condition is often present in the hypertrophied glands of non-fatal chronic infective diseases. In the later stages of many diseases in which the lymphoid tissue shows changes, there occurs a considerable diminution in the number of lymphocytes in the lymphatic glands. They appear to be much less densely packed together, and with the increase in size of the sinuses, which is such a common event, the lymphoid tissue proper is decreased in amount. In such glands the place of the lymphocytes in the follicles is largely taken up by proliferated endothelial cells or by plasma cells when these latter are present in large numbers. This reduction in the lymphocyte content of the gland follicles causes a loss of the normal contrast between the densely packed cortical and more sparsely filled medullary regions of the lymph follicles.

The proportion of lymphocytes met with in film preparations naturally varies with the number of cells of other kinds present. In the case of the normal gland lymphocytes usually form considerably over 90 per cent. of the total cells, in certain pathological conditions they may be reduced to 65-70 per cent., rarely lower.

Evidences of mitosis and direct division were found comparatively rarely in the lymphocytes in film preparations. This was the case not only in those glands obtained from the post-mortem room, but also in the glands from the experimentally inoculated guinea-pigs. Evidences of degeneration (loss of staining affinity, shrinking or breaking up of the nucleus) were more common. Fat droplets were never found in the cytoplasm of these cells, nor was a lymphocyte ever recognized as phagocytic.

C. *The endothelial cells.* An increase in number of the endothelial cells is one of the most constant morbid changes seen in lymphatic glands. This increase may take place in the sinuses, the lymph follicles, or at the germ-centres.

These cells are familiar as the main phagocytes of lymphoid tissue. They ingest bacteria, other cells of every variety, and play a prominent part in the

destruction of red blood corpuscles. Their phagocytic capacity is often very great, and an individual cell of this type may be seen to contain 20-30 red blood corpuscles. In the early stages of infective processes their increase is most marked at the germ-centres and in the gland sinuses, ultimately the increase may be general throughout the gland. Evidences of multiplication are common, and they frequently contain more than one nucleus. They sometimes form a large proportion of the cells seen in films; for example, in a case of septicaemia they totalled 30 per cent., and in two cases of typhoid fever 26 per cent. and 25 per cent. respectively. The commonest variety is the large endothelial cell of the sinuses and is so well known as to require no detailed description. Very similar in appearance are the large phagocytic cells which are seen at enlarged germinal centres.

Another variety, for the inclusion of which under this heading there appears to be some grounds, is a smaller cell often present in large numbers and which is identical with the 'lymphocytoid' cells of certain writers.

This cell is of varying size, usually two or three times the diameter of a small lymphocyte. The cytoplasm stains a deep blue with Leishman's stain, and varies much in amount. The nucleus may be central or eccentric. The nucleus stains less deeply than does that of a lymphocyte, and a delicate nuclear network is frequently to be made out. They are met with in the sinuses, along the septa, and in the lymph follicles and their prolongations. In the latter situations they may be strikingly numerous. In two of my cases they were present in very large numbers. These were instances respectively of acute sepsis in an infant and chronic and acute endocarditis in an adult.

The following reasons appear in favour of their classification as endothelial cells:—They are found in greatest numbers in those glands where endothelial proliferation is most marked. Mitotic figures and evidence of direct division are common. They are phagocytic to lymphocytes, though not to any marked extent. They occasionally contain 2-3 nuclei arranged like those in 'lymphadenoid' giant-cells. Transitional stages between these cells and the common endothelial cells of the sinuses may be made out (Fig. 4, 1).

At times, and especially in those glands in which haemolysis is marked, some of the large endothelial cells contain globules of large size, staining brightly with acid dyes. These are the remains of ingested red blood corpuscles, and all stages in their formation from such corpuscles may be seen.

Small multinucleated cells of the 'lymphadenoid' type (Fig. 4, 5) were frequently met with. As a rule they are few in number, but were increased in those glands which showed marked proliferation of endothelial cells.

Excluding a case of lymphadenoma, these cells were found to be numerous on only one occasion. This was a case of fatal pyaemia due to the influenza bacillus, and in all the glands examined and also in the spleen there was considerable endothelial proliferation with numerous small giant-cells of this type.

Cells resembling the 'polykaryocyte' or small giant-cell of the red bone marrow (as distinguished from the osteoclast or myeloplax) were met with very rarely.

The two cases in which they were present in the glands in large numbers are of interest. The first was a case of pernicious anaemia. Here these cells were found both in the prevertebral glands and also in the glands situated just anterior to the carotid sheath in the neck. They were much more numerous in the latter situation. These glands showed no naked-eye changes, beyond slight enlargement and reddening, to distinguish them from normal lymphatic glands. The more striking histological features were endothelial proliferation, the presence of numerous nucleated red corpuscles, and the presence throughout the sections of a large number of the giant-cells in question. The second case was one of fatal anaemia with marked degeneration and hypoplasia of the red bone marrow. Here the lymphatic glands were numerous, enlarged, and dark red, and contained large numbers of these cells, but in this case they were mainly confined to the gland sinuses (Fig. 5). In both cases these cells corresponded exactly to the polykaryocyte of the bone marrow. They showed the same tendency to shrinkage and pyknosis of the nucleus, the composite, 'basket-like' structure of which was very evident. A few of them were seen to be phagocytic to other cells (Fig. 4, 3 and 4). In one other case of grave anaemia a very occasional cell of similar type was seen in the glands. On no other occasion were they found.

D. *Plasma cells (type of Unna).* These cells were commonly present, often in considerable number, in the glands from cases of acute and chronic infection. In a case of acute septicaemia they were numerous in glands from all parts of the body. They were present in greatest number, however, in glands anatomically connected with an infective focus, e.g. the mediastinal glands in pneumococcal lung infection, the cervical glands in diphtheria.

In such cases they are most numerous in those portions of the lymph follicles which project into the medulla of the gland and which are therefore contiguous to the sinuses. In such situations they take the place of the normally found lymphocyte (Fig. 3). As has been previously recorded by various observers, cells suggesting transitional forms between the lymphocyte and the plasma cell were frequently to be seen.

E. *Polymorphonuclear neutrophils and neutrophilic myelocytes.* The presence of young and adult varieties of the former cell in the lymphatic glands in varying quantities and apart from the occurrence of areas of acute inflammation is well known, and the glands have long been regarded as a possible site of origin for these cells. The occurrence of myelocytes in these situations in any but the smallest numbers, excluding cases of myelaemia, is a rare event. One case is of interest in this connexion. Death was due to sub-acute purulent peritonitis following paracentesis. Masses of dark-red glands of a jelly-like consistency were present in the mediastinum. Film preparations from these glands showed the presence of many polymorphonuclear neutrophils (35.6 per cent.), neutrophilic myelocytes (3.3 per cent.), and transitional varieties (2.8 per cent.). In sections the sinuses throughout the glands were distended and filled with finely granular cells of the above varieties and red blood corpuscles. These cells

were confined almost entirely to the sinuses, and the appearances suggested that the sinuses were possibly acting as a site for their production or multiplication.

F. *Coarsely granular eosinophile cells.* An increase in the number of these cells was seen on several occasions. As a general rule they are more numerous in glands from the body cavities than in those from more superficial situations.

In two cases, one of acute sepsis, the other of diphtheria, they were seen in very striking numbers. In the former case as many as 70-80 could be counted in a single microscopic field ($\frac{1}{8}$ in. objective).

G. *Cells with basophilic granulation.* The basophilic tissue-cell is constantly present in lymphatic glands in varying numbers. They are most commonly found along the course of the gland septa. Large numbers of these cells were seen on several occasions, usually in glands which showed evidences of degeneration. Occasionally a few basophilic cells more closely resembling the mast cells of the blood were seen. Like the eosinophile cells, the basophilic cell is more commonly found in the glands of the body cavities, in particular the group of glands lying along the course of the abdominal aorta.

Little evidence was found that the lymphatic glands play any great part in the phagocytosis of bacteria. The best examples of such phagocytosis were seen in the abdominal glands from cases of typhoid fever, though not even here to any striking degree. In the guinea-pigs inoculated intraperitoneally with cultures of *B. coli*, bacilli were found in distant glands (bifurcation of trachea) in considerable numbers within $1\frac{1}{2}$ hours. Here again there was little bacterial phagocytosis.

In a number of cases films of the gland juice were fixed wet in formalin vapour and stained to demonstrate fat. Droplets giving a reaction for fat with Scharlach R. were present in the endothelial and polymorphonuclear cells in many cases of acute bacterial infection. Such droplets were never found in the lymphocytes.

To summarize briefly, the histological changes met with in the lymphatic glands in the numerous morbid conditions in which these structures show change are as follows:—

In the early stages of acute infective processes we commonly find an increase in size and vascularity. Signs of cell proliferation are seen at the germ-centres and among the endothelial cells in the sinuses and elsewhere. Accompanying these changes the conversion of the gland sinuses into blood sinuses is usually apparent. The glands evidently act as centres for the destruction of red blood corpuscles, for cellular, and, to a less marked extent, for bacterial phagocytosis.

Histological evidence tends to show also that these structures may serve as sites of formation for the majority of the varieties of leucocyte found in the blood. In certain cases the lymphatic glands play a part in the formation of red blood corpuscles, and may show the presence of areas closely resembling the structure of red bone marrow.

In the later stages of fatal infective processes the changes seen are largely

those of degeneration. They consist of reduction in numbers of the lymphocytes, of marked endothelial proliferation, the disappearance of the germinal centres with their replacement by hyaline material, cellular changes suggesting chronic inflammation and fibrosis. The phenomena of erythrocyte destruction is frequently the most striking feature of such glands.

Some Experiments with Gland Fluid.

Recently the lymphoid tissues and bone marrow have come to be regarded as the sites of production of various defensive antibodies or of alexin. Hankin prepared a substance having bacteriolytic powers from extracts of the lymphatic glands and spleen. Levaditi obtained a haemolytic complement from autolysed lymphoid tissue. The early appearance of immune bodies to various bacteria and to red blood corpuscles has been noted in these tissues by Pfeiffer and Marx, Deutsch, Wassermann, and others. Römer found that antiabrin was present in greatest amount in specifically immunized animals in those organs richest in leucocytes. In the course of the present work a number of experiments have been carried out with a view to determining the presence of such antibodies in the lymphatic glands and certain other lymphoid tissues.

Haemolysins and haemagglutinins. Histological evidence suggests that one important function of the lymphatic glands in disease, a function which these structures share with the spleen and bone marrow, is the destruction of red blood corpuscles. It has been shown above that lymphatic glands at some distance from the site of inoculation in an experimentally infected animal may show marked evidences of haemolysis within two hours of inoculation. The question arises whether these phenomena are due to the formation in these localities of some substance inducing haemolysis, or whether their occurrence is dependent upon the local circulatory conditions common to such tissues as the spleen and lymphatic glands. In favour of the latter view are the facts that the red-corpuscle destruction is always most marked in, and sometimes confined to, the regions of the glandular sinuses, and also that very striking examples of haemolysis are frequently met with in glands in which the lymphoid tissue is reduced to a minimum and the seat of extensive hyaline deposits (Fig. 2). The investigation of this question is further complicated by the common occurrence in the glands of haemolytic bacteria, whose haemolytic toxins are remarkably thermostable and resist heating to considerable temperatures.

In certain morbid conditions in man it has been shown that substances exist in the blood serum which cause agglutination and more rarely haemolysis of the red blood corpuscles of normal human beings. The blood serum from such cases can, however, very rarely be shown *in vitro* to produce similar effects on the immune red cells. Yet in such cases histological examination after death often proves the existence of marked haemolysis in the lymphoid tissues.

Two lines of investigation suggested themselves :—

A. In those cases where the blood serum shows an agglutinative or haemolytic action upon normal red cells, can substances with similar properties be demonstrated in the lymphatic glands ?

In a number of such cases, mainly cases of typhoid fever, the blood serum and a number of lymphatic glands were obtained after death. The glands were freed from extraneous fat, pounded up for some time with sterile powdered glass, and the resulting fluid pipetted off and centrifugalized. Examination of films of this fluid showed that a majority of the cells present had undergone disruption. The action of this gland juice, and of the blood serum from the same case, on a 5 per cent. suspension of normal red blood corpuscles in saline were investigated in the usual way and the results contrasted. With one exception the gland juice was found to possess a feebler agglutinative action upon the normal red cells than did the immune blood serum. The single exception was in a case of typhoid fever. Here the juice obtained from the abdominal lymphatic glands rapidly haemolysed normal red corpuscles, both before and after heating to 60° C. for one hour, while the immune blood serum caused only agglutination of the normal erythrocytes. The gland juice, however, was found to contain large numbers of bacilli which would account for the above result, since we know that both typholysin and colilysin are thermostable substances.

B. In those cases where red-cell destruction is evident in the lymphatic glands after death, can the gland fluid be shown, *in vitro*, to possess a haemolytic action on the red blood corpuscles from the same case ? Here the gland juice and blood serum were examined in a similar way as to their action on a suspension of the patient's own red cells. Here again the results were negative.

Haemopsonins. The fluid, obtained in precisely similar fashion from lymphatic glands of cases which showed, *post mortem*, the presence of numerous red glands, and which glands on subsequent examination contained marked evidences of phagocytosis of red corpuscles, was mixed with suspensions of normal red blood corpuscles and of normal leucocytes. Similar experiments were carried out using immune red cells in place of the normal. The amount of red-corpuscle phagocytosis after incubation was noted and contrasted with the results obtained by employing the immune blood serum in place of the gland fluid. The results were invariably negative in that haemopsonin, if present in the immune blood serum, was never demonstrated, to more than a very slight degree, in the gland fluid. The number of observations in this particular connexion was, however, small.

Bacterial agglutinins and opsonins. For the investigation of the presence of these substances in the lymphoid tissues artificially inoculated animals were employed. If the lymphoid tissues especially are concerned in the formation of these substances, then, by choosing suitable time intervals, it might be possible to demonstrate the presence of agglutinins and opsonins for inoculated bacteria, in these situations, either earlier than, or in greater quantity than, in the blood serum of the same animal.

Rabbit A. The blood serum was first examined and found to cause no agglutination of *B. typhosus* in half an hour with a serum dilution of 1 in 10. The rabbit was subsequently inoculated subcutaneously with 100,000,000 of a killed culture of *B. typhosus*. Forty-eight hours later the blood serum agglutinated *B. typhosus* with a serum dilution of 1 in 100. The animal was killed and the agglutinative power of the blood serum (from the heart) compared with that of the fluids obtained by pounding up lymphatic glands, spleen, and bone marrow severally with powdered glass and subsequently centrifugalizing. The blood serum agglutinated *B. typhosus* in a dilution of 1 in 100 in half an hour. In a like dilution, the gland, spleen, and marrow fluids gave no reaction.

The opsonic content of the same three fluids and the blood serum was examined by incubating one volume of each with equal volumes of a suspension of human leucocytes and a suspension of typhoid bacilli.

In the case of the spleen and marrow fluids the amount of phagocytosis was considerably less than in the case of the serum.

The comparative results of the blood serum and the gland fluid were of interest:—

Blood serum + Bacilli + Leucocytes. 50 cells contained 188 bacilli.

Gland fluid + Bacilli + Leucocytes. 50 cells contained 390 bacilli.

In the four animals used for this investigation this was the only instance in which more opsonin was demonstrated in the tissue fluid than in the blood serum.

Rabbit B. After proving the absence of agglutinins for the typhoid bacillus from the blood serum, the animal was inoculated subcutaneously with 200,000,000 of a killed culture of *B. typhosus*. Ten hours later the rabbit was killed.

Agglutination results (employing a suspension of *B. typhosus*):—

Fluid.	Dilution.	Time.	Reaction.
Blood serum	1/20	½ hour	Fair agglutination. Partial loss of motility.
	1/100	"	Very slight agglutination.
Marrow fluid	1/20	"	" "
	1/100	"	No reaction.
Gland fluid	1/20	"	" "
	1/100	"	" "
Spleen fluid	1/20	"	Slight reaction.
" "	1/100	"	No reaction.

In neither lymphatic gland, spleen, nor bone marrow fluid were agglutinins demonstrable in such quantity as in the blood serum.

The opsonic content of these fluids and blood serum were compared as in the preceding case, the results showing a considerable excess of opsonin in the serum over any of the other fluids.

Further observations on the presence of opsonins in the lymphoid tissues were made by inoculating two guinea-pigs with respectively living and dead cultures of the colon bacillus. The animal which received the injection of living bacilli was killed after four hours; the one which was inoculated with the dead culture, at the end of thirty-six hours. In both cases inoculations were intraperitoneal. The subsequent technique was similar to that employed in the former experiments. In both animals more opsonin was demonstrable in the

blood serum than in the fluids obtained from lymphatic glands, spleen, or bone marrow.

In the same way the opsonic content of the fluid obtained from a number of human lymphatic glands was estimated and compared with that of the corresponding blood sera. In all of these cases the blood serum proved the richer in bacterial opsonins.

Though the above experiments are too few in number to permit of definite conclusions they tend to show that antibodies and allied substances, demonstrable in the blood serum, are not easily demonstrable as such in the lymphoid organs in other than slight amounts. Again, these experiments favour the view that the phagocytosis of erythrocytes, so commonly met with in these tissues after death, is independent of any specific substance formed by the tissue proper.

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DESCRIPTION OF FIGURES.

FIG. 1. Drawing of a portion of the peripheral blood sinus from prevertebral gland of domestic pig. In the midst of the blood are islets of cells of various type. The three aggregations of small cells with dark nuclei consist of nucleated red cells. Other islets are composed of cells resembling myelocytes. Cells with eosinophile granules are scattered through the drawing, while at the upper part a portion of one of the lymph follicles is shown.

Leishman's stain. $\frac{1}{6}$ " objective. No. 1 eye-piece.

FIG. 2. Drawing of one of the prevertebral glands from a case of chronic sepsis. The sinuses are widely distended and filled with blood and endothelial cells packed with red blood corpuscles. (Details not visible under low power.) The lymphoid tissue is much reduced in amount and the site of considerable deposits of hyaline material.

Leishman's stain. $\frac{2}{8}$ " objective. No. 1 eye-piece.

FIG. 3. Drawing of a portion of a lymphatic gland showing replacement of the lymphoid cells in a follicle by plasma cells. These cells are most numerous at the periphery of the follicle and contiguous to the distended sinuses which contained blood and phagocytic endothelial cells.

(From a guinea-pig killed some weeks after inoculation with a portion of a human lymphadenomatous gland.

Stained with haemalum and eosin. $\frac{1}{6}$ " objective. No. 1 eye-piece.

FIG. 4. A drawing of some of the types of cells met with in lymphatic glands. At 1 are shown several of the cells which occur commonly in the glands of many morbid conditions and which appear to be small endothelial cells. At 2 are two of the common endothelial cells of the lymph sinuses. 3 and 4 are two types of the giant-cells met with occasionally, and resembling similar cells of the red marrow. 5 is a smaller giant-cell of the lymphadenoid type. For purposes of comparison two small lymphocytes are also included.

Leishman's stain. $\frac{1}{12}$ " oil-immersion objective. No. 1 eye-piece.

FIG. 5. Microphotograph of one of the sinuses of a gland from case of fatal anaemia with hypoplasia of bone marrow. Giant-cells resembling those of bone marrow are shown. Their nuclei show considerable variations.

Leishman's stain. $\frac{1}{8}$ " objective. No. 1 eye-piece.

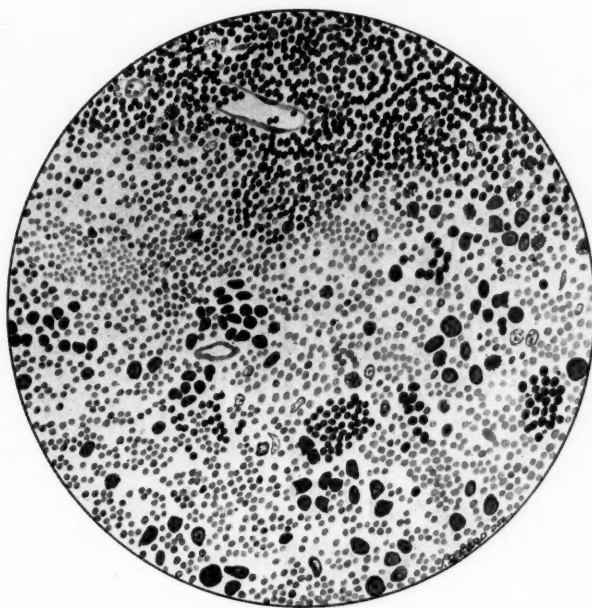


FIG. 1



FIG. 2

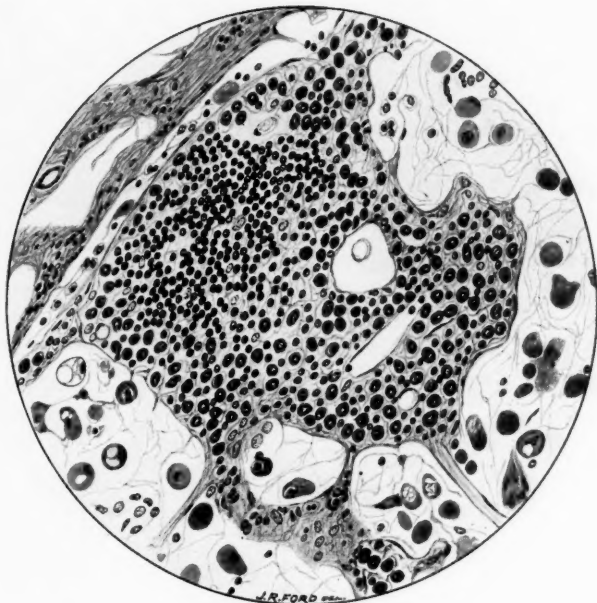


FIG. 3

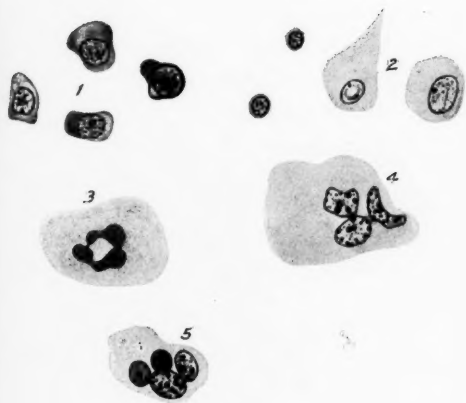


FIG. 4

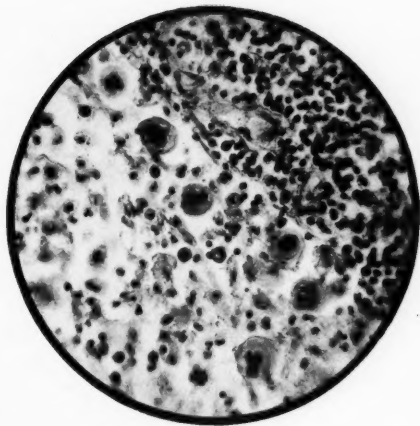


FIG. 5

CRITICAL REVIEW

LACTIC ACID IN METABOLISM

By J. H. RYFFEL

PART II

LACTIC ACID IN PATHOLOGICAL CONDITIONS

Introductory.

FROM evidence given in the first part of this review it may safely be concluded that lactic acid is an intermediate product in the metabolism of carbohydrate and of some of the constituents of protein, which is present in small quantities in all tissues and in blood during normal life. It is probable that the immediate precursor of lactic acid in the liver (44) and in muscle (9) is some intracellular complex. This view as to the liver is dependent on aseptic autolytic experiments, the value of which has been rendered somewhat doubtful by the recent discovery by Wolbach and Saiki of an anaerobic spore-bearing bacterium commonly present in the livers of healthy dogs, which does not grow in ordinary cultures. As to muscle, however, the principal support of this view is derived from experiments on surviving cold blooded muscle, in which it is possible to cause the formation and disappearance of lactic acid by alternately tetanizing the muscle and keeping it in oxygen, and to continue the process almost indefinitely without reducing the final yield of lactic acid on the production of heat rigor. The total yield of lactic acid thus obtained is greater than could be formed from the glycogen of the muscle, so that the phenomenon is best explained by the partial breaking down and resynthesis of an intracellular complex in the living muscle.

Though lactic acid is almost certainly present in normal urine, its quantity is very small, so that no observer has succeeded in demonstrating its presence by the formation of the zinc salt after ether extraction. The concentration of lactic acid in the urine, moreover, is less than that in blood, so that the lactic acid of normal urine should be considered rather as the result of a small amount of leakage from the kidney cells, which themselves contain lactic acid, than as the result of an actual excretion. When the lactic acid of the blood rises above a certain limiting value, which is not yet determined, but which in man must be less than 0.7 per mille and greater than 0.2 per mille, active excretion

by the kidneys takes place, so that the urine may contain much more lactic acid than the blood, 5 per mille being easily obtained by violent exercise. This lactic acid is not present as such in the urine, being largely neutralized by bases, the excretion of which is increased at the same time (34). The occurrence of lactic acid in the urine is therefore very similar to that of sugar, which is normally present in traces in the urine, but is actively excreted by the kidneys when there is sufficient hyperglycaemia.

Accumulation of lactic acid in the blood sufficient to cause its active excretion may be due to any of the following causes:—

I. *Increased formation by the muscles due to their activity.* This is the case in violent muscular exercise, where it is not normally due to an inadequate supply of oxygen to the blood, as administration of pure oxygen immediately before and after a short period of running (2 to 3 minutes) has no noticeable effect on respiration, pulse, or the output of lactic acid in the urine.

II. *Diminished supply of oxygen to the tissues.* Within physiological limits this is not, at rest, as effective a cause of the excretion of lactic acid in the urine as I, but a combination with I is most effective.

III. *Diminished power of using oxygen.*

IV. *Absorption of lactic acid from the alimentary canal* may be sufficient to cause its appearance in the urine. This has been shown to be the case in man by Ryffel (35). Mixed inactive lactates of sodium, potassium, and calcium, containing 8 gm. lactic acid, taken by the mouth, led to the excretion of 0.49 gm. lactic acid in the urine in 6.5 hours, in which time the normal lactic acid output would have been 0.02 to 0.03 gm. Neubauer, after injecting 2.5 to 4.5 gm. sodium inactive lactate per kilo subcutaneously into rabbits, observed an increase in the ether soluble acids of the urine amounting to 5 to 29 per cent. of the lactic acid injected, and isolated pure zinc inactive lactate from the ether extract.

V. *An excessive supply of carbohydrate* leads to the formation of lactic acid. Mayer obtained a definite yield of zinc lactate from the urine of rabbits after injecting inosite subcutaneously. Harley found that injection of about 10 gm. glucose per kilo into the circulation of dogs with ligatured ureters caused the gradual onset of coma with occasional muscular tremors and even convulsions. The lactic acid of the blood was slightly increased, reaching its maximum one hour after the injection and then falling very slowly. The blood also contained alcohol, acetone, and diacetic acid. The urine obtained in twelve hours after removing the ligatures contained 0.115 and 0.173 gm. lactic acid. Unfortunately he does not state how the lactic acid was identified. He suggests that the formation of lactic acid from glucose took place in the liver, as the lactic acid of the liver was very high two hours after the injection. An experiment in which alimentary glycosuria increased the lactic acid of the urine will be described under diabetes. Asher and Jackson found that injection of sugar into the circulation did not alter the small increase of lactic acid in the blood

obtained from dogs, when the arterial supply of the abdominal organs and kidneys was ligatured, and thus confirmed Harley's view that the transformation of glucose to lactic acid in his experiments took place in the liver.

VI. *Impaired liver function.* The experiments of Minkowski on geese, and of Salaskin and Zaleski on dogs, in which lactic acid appeared in the urine after extirpation of the liver, are supposed to show that the liver normally acts in preventing the accumulation of lactic acid in the blood by transforming it into some other substance. Wiener showed that an oxidation product of lactic acid, tartronic acid, is necessary for the synthesis of uric acid in birds. von Noorden holds that the transformation of lactic acid to glucose, which takes place in the diabetic animal, is a normal function of the liver, by means of which the lactic acid, poured into the circulation in muscular activity, is again rendered available as a food material.

The toxicity of lactic acid when neutralized is scarcely if at all greater than that of a corresponding amount of glucose, the injection of 1 to 1.5 gm. sodium lactate per kilo into the circulation of dogs producing no symptoms of intoxication (6). The occurrence of abnormal quantities of lactic acid in the urine is, therefore, only of pathological significance as an indication that oxidation is incomplete and that some degree of acidosis exists. The ammonia of the urine, the acidity of the blood, and the percentage of carbon dioxide in the alveolar air are the best guides as to whether the acidosis is sufficient to cause pathological symptoms.

From the account which follows it will be seen that those pathological conditions, which favour the appearance of lactic acid in the urine, also tend to cause an increase in the excretion of the acetone bodies, that in fact the appearance of these two groups of bodies is the result of the same phenomenon, imperfect oxidation. Lactic acid belongs to the metabolism of carbohydrate and protein, the acetone bodies to that of fat, so that a well-fed animal will tend to excrete lactic acid and sugar, a starved animal acetone bodies. This is the case also with experimental shortage of oxygen. If a well-fed animal is sufficiently starved of oxygen, sugar and lactic acid appear in the urine. Ryffel, however, in an experiment on man in which the supply of oxygen was considerably restricted for one hour, found both acetone and oxybutyric acid in the urine (34). Reale and Boeri, by restricting the respiration of dogs, obtained a small but definite increase in the acetone of the urine.

Lactic Acid and excessive Muscular Activity.

In *epilepsy* lactic acid regularly makes its appearance in the urine passed after the attacks, if these attacks are sufficiently violent. Araki obtained pure zinc lactate from the urine, passed after an attack by a typical case of epilepsy, on two out of three occasions. The largest amount of zinc lactate was 1 gm. from 227 c.c. urine. Inouye and Saiki investigated six cases of typical epilepsy

and in every case obtained pure zinc lactate from the urine passed one to two hours after the attack, the largest yield from the urine of one attack being 2 grm. zinc lactate. The zinc salt was shown to be that of sarcolactic acid by complete analysis, determination of the water of crystallization, and determination of the rotatory power. Sugar was always absent, albumin present only in traces. The output of uric acid was increased. They concluded that the principal factor in the production of lactic acid was deficient oxygenation of the blood due to fixation of the respiratory muscles during the fits. However, the absence of sugar from the urine and the presence of only small quantities of albumin indicate that the deficiency of oxygen is not very great, so that the main factor must be the muscular activity, the effect of which is exaggerated by deficiency of oxygen where it exists. This view is confirmed by the observation of Donath that the cerebro-spinal fluid of an epileptic contained no lactic acid that could be isolated as the zinc salt.

A similar explanation will account for the appearance of lactic acid in the urine of frogs after poisoning with *strychnine* and with *veratrine* and the large yield (0.3 per cent. zinc lactate) of lactic acid obtained from dog's blood after *veratrine*. The deficiency of oxygen, however, appears to be greater, as glycosuria is frequent in mammals with both these drugs. In the blood of a rabbit poisoned with strychnine Minkowski (26) found the carbon dioxide reduced to less than one-half the normal, presumably owing to the abnormal quantity of acid present.

The acidity of the blood is higher than normal in *pyrexia*. When the patient is not starved this is probably partly due to the presence of excess of lactic acid, but the excess must rarely be sufficient to cause the excretion of lactic acid by the kidneys. Jerusalem found 0.25 lactic acid per mille in the urine of a patient with high fever. Minkowski (26) found that the arterial blood of dogs with artificial septic fever contained less carbon dioxide and more lactic acid than normal (0.018 per cent. zinc lactate, normal 0.006 per cent.).

Lactic Acid and Pregnancy.

From the urine of 17 cases of *eclampsia* Zweifel obtained zinc sarcolactate without exception, sometimes only in traces, but mostly in considerable quantity up to 1 per mille. The presence of an unusual amount of acid in the blood was confirmed by the fact that the ammonia nitrogen of the urine was increased at the same time, forming in one case 16.5 per cent. of the total nitrogen. Lactic acid was found in the urine before the fits in four cases. Moreover, on comparing maternal venous blood, blood from the cord of the living child, and placental blood, he found more lactic acid in the cord and placental blood than in the maternal blood in three cases. Thus, in one case the maternal blood yielded 0.09 grm. zinc lactate per mille, the cord blood 0.26

per mille, while the maternal urine contained only a trace. In most cases, however, the maternal blood contained more lactic acid than that of the child. Thus, in one case the maternal blood yielded 0.09 and 0.15 per mille, while neither the cord nor the placental blood yielded any zinc lactate. His conclusion, that lactic acid comes from the child and is the cause of the symptoms of eclampsia, is scarcely warranted by these results. A. ten Doesschate, on the other hand, found more lactic acid in the maternal venous blood than in that of the dead child or in the placenta, and concluded that the lactic acid, which was present in small quantity in the urine, was due to the convulsions of eclampsia, and that it was impossible to draw conclusions from minute differences in lactic-acid content of blood owing to the inadequacy of the ordinary ether extraction method, which both he and Zweifel employed. Donath also concluded that the lactic acid in the urine of eclamptics was due to the convulsions and came from the muscles.

Muscular activity together with impeded respiration will account for the lactic acid and increased acidity, which have been observed in the urine of cases of *prolonged but otherwise normal labour*, as recorded by Vicarelli and Doesschate. Such an explanation, however, cannot account for the observation by Underhill of a relatively large quantity of sarcolactic acid in the urine of a case of *pernicious vomiting of pregnancy*. The 24 hours' urine of this case, which was fed with rectal enemata only, yielded on one occasion 1.2 grm. zinc lactate, shown by analysis and by the polariscope to be the salt of sarcolactic acid. The ammonia nitrogen of the same urine amounted to 32.7 per cent. of the total nitrogen, so that the acidosis of the case was of a high order. On the uterus being emptied, the ammonia nitrogen fell in three days to 3.2 per cent. of the total nitrogen, and the lactic acid disappeared. Similar high values for ammonia have been found by Williams, who concludes that this disease involves an acute atrophy of the liver. The acidosis observed is not entirely due to lactic acid, as the acetone bodies also occur. Lactic acid has been found in the urine of cases of *nephritis with pregnancy* (55), (5). There is, therefore, in pregnant women an increased tendency to pass lactic acid in the urine, but whether this is primarily due to production of lactic acid by the foetus, or to impaired liver function, it is impossible to say at present (21).

Lactic Acid and Diminished Oxidation.

Many observers have sought for lactic acid in the blood and urine of patients, in whom, from circulatory or respiratory disturbance, or from diminished haemoglobin in the blood, the supply of oxygen to the tissues is presumably diminished, but the results have up to now been far from convincing. That the occurrence of lactic acid in the urine of these cases should be rare is indicated by the fact that reduction of oxygen in the air breathed, sufficient to

lower the alveolar carbon dioxide considerably, does not in man cause excretion of lactic acid in the urine within limits that can be voluntarily endured. Moreover, in the majority of these cases reduction of the alveolar carbon dioxide is by no means marked. Fitzgerald made a great number of observations on cardiac, pulmonary, and anaemic cases, and found that except in cyanosis the average values for alveolar carbon dioxide were but little lower than the average normal mean. In individual cases the values were occasionally below the minimum, e.g. the alveolar carbon-dioxide pressure of a woman with secondary anaemia (haemoglobin 23 per cent.) was 29.8 mm. of mercury, while the normal minimum for woman is 30.4 mm. No case of pneumonia with cyanosis before the crisis, and no case of pernicious anaemia with less than 42 per cent. haemoglobin, was investigated. The cases with cyanosis showing alveolar carbon dioxide below the normal mean were polycythaemia, mitral stenosis, and congenital pulmonary stenosis. The lowest value, 21.1 mm. carbon dioxide, was obtained from a girl with the last disease.

Schütz obtained crystals of a zinc salt, which by analysis he found not to be the lactate, from a number of cases including pneumonia, phthisis, heart failure, and pernicious anaemia. In the urine of *pernicious anaemia* Hoppe Seyler found lactic acid in one case. von Noorden found lactic acid in one case, but not in another, nor in two cases of post-haemorrhagic anaemia. Ryffel found the output of lactic acid only slightly greater than normal in the urine of a case of pernicious anaemia with haemoglobin 20 per cent.

Nencki and Sieber failed to obtain zinc lactate from the urine of a case of *leukaemia*, and pointed out that the crystals of supposed zinc lactate obtained previously had not been analysed.

French, Pembrey and Ryffel found an apparent increase of lactic acid over the normal in the urine of two cases of *congenital heart-disease* with cyanosis, who were sufficiently well to do light work, but who both showed reduced alveolar carbon dioxide. Ryffel has since, however, examined the urine of five cases of *heart-disease*, all of whom were in bed, one case, a boy of 13, being markedly cyanosed, without finding an output of lactic acid above the normal. A boy of six with pneumonia but no marked cyanosis showed no increased output of lactic acid, but both acetone and diacetic acid were present in the urine in spite of a diet of nearly two pints of milk. These bodies disappeared as the patient recovered. From the urine of a case of dyspnoea with cyanosis ten Doesschate obtained a small yield of nearly pure zinc lactate.

It thus appears that in these cases the lactic acid of the blood rarely rises high enough to cause active excretion by the kidney. The lactic acid of the blood during life has been found increased in heart-disease by Zülzer, but it is in the cyanosis of acute pulmonary disease that the highest values of lactic acid should be expected, as the tissues are usually well nourished to start with, and metabolism is even higher than normal owing to the pyrexia. Both Salomon and Irisawa found more lactic acid in the post-mortem blood of cases of pneumonia and other pulmonary diseases with cyanosis than in other cases.

Lactic acid has been observed in the urine of man and animals as a result of *carbon-monoxide poisoning*. Münzer and Palma investigated the case of a man, who was found in deep coma as the result of spending fourteen hours in a room the air of which was contaminated with the fumes of a charcoal stove. In the urine obtained by catheter they found sugar, acetone and a little albumin. That of the next 24 hours contained 8.92 gm. nitrogen, ammonia nitrogen 6.2 per cent., uric acid nitrogen 12.4 per cent., and yielded 0.87 gm. zinc sarcosylactate, which was identified by analysis. The urine of the next three days contained 13 gm., 21 gm., 25 gm. nitrogen respectively, although no food was given till the third day. The ammonia and uric acid fell to normal, and the lactic acid practically disappeared on the third day.

Experiments on animals have shown that the poisonous action of carbon monoxide is due to the formation of carboxyhaemoglobin, which diminishes the carrying power of the blood for oxygen, and, therefore, the supply of oxygen to the tissues. This causes an accumulation of lactic acid in the blood, which is thereby rendered more acid than normal. Respiration is increased, the carbon dioxide of the blood reduced, and an acid urine containing lactic acid excreted. If the animals are well fed sugar is present in the urine, but not if they have been starved for several days previously. The glycogen of the liver is reduced. Excretion of ammonia and amino acids is increased. Araki obtained large yields of pure zinc sarcosylactate from the blood and urine of dogs and rabbits, which had been poisoned with carbon monoxide for four to ten hours. The highest yields were—from rabbit's urine after ten hours 1.38 gm. zinc lactate, from dog's blood 0.49 per cent. zinc lactate. The alkalinity of the blood in several experiments was much reduced. The urine passed by normal rabbits and dogs, after subcutaneous injection of sodium inactive lactate, was strongly alkaline and contained only traces of lactic acid. That passed by carbon-monoxide-poisoned animals with the same treatment was acid, or neutral, and contained much lactic acid, which was partly inactive, partly sarcosylactate. Thus a dog, which received 5.14 gm. sodium lactate subcutaneously and was poisoned for eight hours, passed urine which yielded 4.93 gm. zinc lactate. From these results Araki concluded that the lactic acid of carbon-monoxide poisoning was due to diminished oxidation, and not to impaired liver function. The output of urea on the day of poisoning was greater in both starved and fed animals than on normal days. Saiki and Wakayama showed that carbon monoxide reduces the carbon dioxide and oxygen, and increases the lactic acid of the blood of both rabbits and dogs. Thus the arterial blood of a dog after poisoning for $4\frac{1}{2}$ hours contained 3.3 per cent. carbon dioxide, 2.0 per cent. oxygen, 0.1 per cent. lactic acid. The average figures for normal dog's blood are—carbon dioxide 35 per cent., oxygen 20 per cent., lactic acid 0.03 per cent. Saito and Katsuyama found lactic acid in the urine of fowls after poisoning for three to five hours.

Recently Kennaway, Pembrey, and Ryffel have investigated the effect of carbon monoxide on gaseous exchange and formation of lactic acid in rabbits. Some of their results are given in the following table:—

Rabbit	In grammes.			By Volume.	Remarks.
	H ₂ O	CO ₂	O ₂	$\frac{\text{CO}_2}{\text{O}_2}$	
I	0.59	0.84	0.71	0.86	30' Normal
	0.20	0.28	0.24	0.85	10' Normal
	0.37	0.45	0.18	1.85	20' Going under CO
III	0.31	0.60	0.42	1.04	30' Normal
	0.07	0.14	0.10	1.02	7' Normal
	0.44	0.22	0.15	1.07	10' ? Quickly fatal CO
IV	0.39	0.65	0.55	0.86	30' Normal
	0.10	0.17	0.15	0.83	8' Normal
	0.22	0.26	0.07	2.70	17' Slowing fatal CO
VI	0.73	0.87	0.70	0.90	30' Normal
	0.62	0.78	0.62	0.92	30' (15' CO)
	0.74	0.86	0.48	1.30	30' CO
	0.91	0.95	0.66	1.05	30' recovering
	0.88	0.91	0.80	0.83	Period of recovery of 3 hours calculated for 30'

These results show clearly that carbon monoxide causes a decreased absorption of oxygen. The deficiency of oxygen causes increased respiration, probably owing to the production of lactic acid, the acidity of which stimulates the respiratory centre, with the result that carbon dioxide is washed out from the blood, as indicated by the high respiratory quotients obtained. During the period of recovery the absorption of oxygen gradually rises and the carbon dioxide of the blood returns to its normal value, so that there is a retention of carbon dioxide with a low respiratory quotient.

Blood, obtained after death from ten to forty minutes' administration of carbon monoxide, contained two to three times as much lactic acid as the blood of rabbits killed by concussion. The urine found in the cage and in the bladder after death contained no more lactic acid than normal. That this absence of abnormal lactic acid was due to the rapid onset of death, was shown by the fact that the urine of those rabbits which survived always contained more lactic acid on the day of experiment than on normal days in spite of reduced feeding. Thus the lactic acid per diem in the urine of rabbit I rose from the average normal value of 18 mg. to 55 mg. on the day of experiment. Sugar was not present in these urines, but made its appearance, with larger quantities of lactic acid, when the administration of carbon monoxide was continued for four hours. In the longer experiments the animal passed through a stage, in which the respirations were very rapid and convulsions were liable to occur, to one of almost complete unconsciousness with slow deep respirations, in which it was very insensitive to increasing doses of carbon monoxide. Rectal temperature at the end of this period was reduced as much as 7°C. A similar condition of coma has been observed in man, when owing to slow accumulation of carbon monoxide

death has not taken place at an early stage. This condition is probably due to the establishment of a lactic acid acidosis.

The urine of animals poisoned with large doses of *amyl nitrite* contains lactic acid often in considerable quantity. Thus Araki obtained 2.1 gm. zinc lactate from a rabbit in six hours. If the animal is well fed, sugar also appears. Saiki and Wakayama found that, four hours after the injection of 0.7 c.c. *amyl nitrite* subcutaneously into a rabbit, the carbon dioxide of the blood was reduced to less than half the normal, and the oxygen to two-thirds. As methaemoglobin is formed in the blood stream the reduced oxygen capacity of the blood and the lowered blood pressure will probably account for the effects observed.

Morphine and *cocaine* cause the appearance of lactic acid as well as sugar in the urine of rabbits (1). The explanation of this action is uncertain. Filehne and Kionka found a reduced intake of oxygen and output of carbon dioxide in animals under morphine narcosis. The oxygen of the blood was lower than normal, but the carbon dioxide, instead of being reduced owing to the lactic acid, was at least as high as the normal, thus indicating a considerably reduced activity of the respiratory centre.

Lactic acid and occasionally sugar occur in the urine of animals poisoned with hydrocyanic acid in repeated small doses (53). The lactic acid of the blood is very high (0.5 per cent. zinc lactate in a dog). The carbon dioxide of the arterial blood diminishes to about half the normal in a few minutes, while the oxygen of the arterial blood remains nearly normal, and that of the venous blood rises, till it becomes nearly equal to that of the arterial blood. The output of carbon dioxide is high at first and then falls, while the intake of oxygen is low throughout in spite of the convulsions (11). The production of lactic acid is, therefore, due to the inability of the tissues to use the oxygen supplied to them by the blood. The high initial output of carbon dioxide and low carbon-dioxide content of the blood are due to the accumulation of lactic acid, which increases the acidity of the blood.

The presence of sarcolactic acid in the urine of patients poisoned with *phosphorus* was first shown by Schultzen and Riess in 1869. They examined a series of nine cases, in five of which lactic acid was present. This was isolated as the zinc salt, which gave correct analyses. Lactic acid was present only in the fatal cases, and was most abundant from the third to the fifth day of the disease. Later work has shown the presence of other abnormal products besides lactic acid in the urine of phosphorus poisoning. Sugar is seldom present (6 times in 141 cases), but alimentary glycosuria exists in 69 per cent. of the cases, when the liver has become enlarged and jaundice is established. Acetone, which regularly occurs, is characteristic of the disease and not due to starvation, as it appears in the first few hours and increases in spite of carbohydrate feeding. Diacetic acid also occurs, but oxybutyric acid, although probable, has not been proved to be present (28), (46), (42). The excretion of nitrogen is low in the first stage, even when the starvation is considered, but rises usually by the third day to 10 to 18 gm. per diem. At this stage the uric

acid may be slightly higher than normal. The urea nitrogen is low (70 to 80 per cent.). The high value of the ammonia nitrogen, 10 to 18 per cent. of the total nitrogen, is due to the formation of an abnormal amount of acid, lactic, phosphoric, sulphuric, and diacetic acids, as its amount can be reduced by the administration of sodium bicarbonate, and the ammonia nitrogen of the rabbit, which remains low when acid is administered, is not appreciably increased by phosphorus poisoning (28). The excretion of amino acids is increased, so that tyrosine and even leucine have been isolated from the urine. There is no reduction in the number of red corpuscles and very little in the amount of haemoglobin of the blood, but the acidity of the blood is increased and the carbon dioxide reduced.

Numerous experiments have been performed on animals to elucidate the problems of phosphorus poisoning. Meyer found that the blood pressure of rabbits poisoned with phosphorus was low, and the carbon dioxide of the arterial blood reduced even to one-third of the normal, while the oxygen remained nearly normal. Araki showed that lactic acid appeared in the urine of dogs and rabbits only in the later stages of acute poisoning. When a small dose was given, it did not appear till about the fourth day. By this time the haemoglobin of the blood was slightly reduced, but not sufficiently to account for the appearance of lactic acid. Sugar, which was absent from all the urines except one, readily appeared when the phosphorized animal was poisoned with carbon monoxide. Neubauer confirmed the older observations, that glycogen rapidly disappeared from the liver in phosphorus poisoning, and showed that giving sugars per os had very little effect in preventing this disappearance. By comparing the increase in the ether soluble acids of the urine, produced by injecting sodium lactate into phosphorized animals, with the increase obtained with normal animals he came to the conclusion that fermentation lactic acid was as easily destroyed in the phosphorized as in the normal animal. The method employed is too unreliable to justify such a conclusion, especially as he obtained relatively larger yields of zinc lactate from the phosphorus urines than from the normal. His results, however, do show that the phosphorized animal can use a very considerable proportion of the injected lactate, although this proportion is almost certainly less than in the normal. Mandel and Lusk showed that phloridzin glycosuria causes the practical disappearance of lactic acid from the urine and blood of dogs poisoned with phosphorus, and that phosphorus causes no further increase in the nitrogenous metabolism of a dog with phloridzin glycosuria. They concluded that phosphorus had the same effect in increasing nitrogenous metabolism by partially preventing the utilization of lactic acid as that of phloridzin by preventing the utilization of glucose. When the precursor of lactic acid, namely glucose, was already useless, phosphorus had no further effect. Several observers have found general metabolism reduced. Welsch observed a decrease of 11 to 20 per cent. in the gaseous exchange and the output of heat. On the other hand, Lusk found that poisoning with phosphorus caused pyrexia and a slight increase in the carbon-dioxide output of a fasting dog, until the day of death, when both the temperature and the carbon dioxide fell.

All these data do not seem to advance our knowledge of phosphorus poisoning very far, but a few points stand out. In phosphorus poisoning there is a *partial* failure of oxidative processes, not due to a diminished supply of oxygen to the tissues, which leads to the accumulation of two principal groups of products of incomplete oxidation, the acetone bodies and lactic acid, which being acid cause a fall in the carbon dioxide of the blood and a rise in the excretion of ammonia. The difficulty with which the oxidative processes are conducted appears to cause a reaction, so that there is an increase, until a short period before death, in carbohydrate, nitrogenous, and possibly also in fat metabolism, which at least compensates for the incomplete nature of the oxidative processes.

As to lactic acid, experimental poisoning with *arsenic* is similar to that with phosphorus and presents the same problems. Meyer showed that arsenic lowers the carbon dioxide of blood and obtained from the blood a zinc salt, which gave correct analyses for a lactate, but was not optically active. Araki also obtained an optically inactive lactate. Morishima, however, showed that acute arsenic poisoning in cats increases very considerably the lactic acid of the blood, liver, and kidneys, and obtained the dextrorotatory or sarcolactic acid on every occasion. Heffter's observation, that arsenic poisoning increases the lactic acid of muscle, while phosphorus reduces it, is of no value owing to his treating the fresh muscle with alcohol. By this method he found that muscle contains as much lactic acid when fresh as after rigor, and that tetanus of isolated muscle reduces the lactic acid in it, which is now known to be the reverse of the truth.

From the urine of cases of *acute atrophy of the liver* Schultzen and Riess first isolated sarcolactic acid. The metabolism of the disease is very similar to that of phosphorus poisoning. Soetbeer found acetone and diacetic acid constantly present in the urine. The ammonia nitrogen was high and was reduced on giving alkali by the mouth.

Neither lactic acid nor oxybutyric acid has been found in the urine after *chloroform* and *ether* anaesthesia, but sugar, glycuronic acid, acetone, and diacetic acid occur. An increase of the total acids, total nitrogen, and unoxidized sulphur of the urine has been observed (19), (3). The urine is therefore very similar to that in conditions where lactic acid occurs, but in man the tendency to produce lactic acid is reduced by the customary starvation before the administration of an anaesthetic.

Lactic Acid in other conditions.

The presence of lactic acid in the urine of a case of *trichinosis* was proved by Wibel. Muscular irritation is probably the cause of its appearance.

Crystals of a zinc salt supposed to be the lactate have been obtained from the urine of cases of *osteomalacia*, but neither Heuss nor Hofmann could prove the presence of lactic acid in large quantities of the urine.

von Noorden has observed considerable quantities of lactic acid in the urine of occasional cases of *cancer* and of *cirrhosis* of the liver. In the former disease

the occurrence of lactic acid may be due to absorption of lactic acid formed by fermentation in the stomach, when this organ is affected by growth. In the latter the disturbance of liver function must presumably be the cause.

Lactic Acid in Diabetes.

Lactic acid being an intermediate product in the metabolism of carbohydrate, the question of its occurrence in diabetic urine is of special interest. Bouchardat stated that he had often found lactic acid in the urine of diabetics, but his method was not a reliable one. Nencki and Sieber obtained a small quantity of zinc salt, the analysis of which did not correspond with that of zinc lactate, from the urine of a diabetic patient collected for four days, when 20 grm. sodium lactate was being administered daily. Stadelmann found lactic acid in the urine of a diabetic who was taking 4.5 grm. lactic acid daily, but could not find it in the urine of other cases who were taking no lactic acid. von Noorden found no lactic acid in the urine of severe diabetics on three occasions. On the other hand, Ryffel found lactic acid in small quantity, but much more than normal, in the urine of four diabetics (35). The lactic acid was estimated by the method previously described after separation by ether extraction. The highest yield was 0.65 grm. lactic acid per diem from the urine of a man, who was passing ten to twelve pints of urine, containing about 7 per cent. of sugar. The normal output of lactic acid determined by the same method with ether extraction was less than 0.02 grm. A case under a carbohydrate-free diet, whose urine contained no sugar, gave 0.16 grm. lactic acid per diem. Administration of lactates equivalent to 10.5 grm. lactic acid per diem to another case increased the lactic-acid excretion from 0.37 grm. to 1.19 grm., a rather larger proportion of the lactic acid given being excreted than in the normal. Two attempts were made to render a normal person glycosuric by means of a large carbohydrate meal. On one occasion the urine gave no reduction and the lactic acid was normal. On the other occasion, the urine reduced Fehling's solution, but probably only contained glycuronic acid. The lactic-acid output per hour for 4½ hours, determined after treating the urine with lead acetate and ammonia, was almost five times as great as the normal. The lactic acid of glycosuric urine seems, therefore, to be a direct result of hyperglycaemia, and is relatively unimportant.

When salts of lactic acid are given by the mouth in diabetes, the lactic acid retained is treated in much the same way as sugar. The output of sugar is not reduced, and may be definitely increased, while the total nitrogenous excretion is practically unaltered. The bases given with the lactic acid serve to reduce the output of ammonia and increase temporarily the excretion of acetone bodies (47). von Noorden gives a case in which 100 grm. of sodium lactate per diem increased the sugar of the urine from 25 to over 50 grm. per diem. It is probable, therefore, that the diabetic transforms lactic acid into sugar just as the depancreatized dog does.

Although there is no special failure to deal with lactic acid in diabetes, there is no evidence that lactic acid forms a source of energy which in any way compensates for the decreased ability to use sugar. This fact need not be taken as showing that lactic acid is not an important intermediate product in carbohydrate metabolism, as the utilization of lactic acid formed within the cell is a very different matter from its utilization when in the circulation.

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